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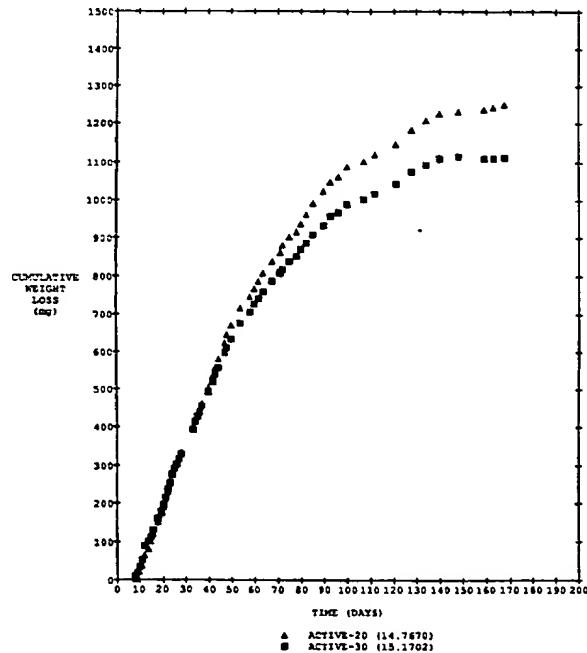
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(54) Controlled release drug delivery device comprising a polymer matrix and a plasticizer.

(57) There is disclosed a slow release drug delivery device for the prolonged administration of topically active medicines which consists of a vehicle in which water is soluble and in which is dissolved the topically active drug which is formed into a stable organogel with a polymer matrix with a very low water absorbing capability. The organogel, in the presence of water or atmospheric water vapor, slowly imbibes such water into the vehicle and by doing so the vehicle becomes incompatible with the matrix and is slowly expelled therefrom. The vehicle dissolves the drug and the vehicle/drug combination is slowly pumped out of the polymeric matrix with substantially linear drug delivery occurring for periods in excess of 6 months. The drug delivery device may be used to administer drugs topically, as a collar or trans dermal patch, orally, as a slow delivery device, particularly as a ruminal bolus, or as a suppository or a subcutaneous implant. The preferred form for the drug delivery device is as a flea and tick collar for household pets and the preferred active drug is selected from the avermectin and milbemycin families of active antiparasitic agents.

FIGURE 4
CUMULATIVE WEIGHT LOSS



EP 0 537 998 A1

BACKGROUND OF THE INVENTION

The use of flea and tick collars is well known with most commercial versions of such devices being of the vaporization type where the active drug is slowly released from the polymeric collar in the form of a vapor. In European Patent Application 90446 a polymeric support material is combined with a plasticizer and a carrier for a pyrethroid contact pesticide, which may be volatile or non-volatile, where the carrier is incompatible with the polymer. The carrier is in the form of a chlorinated hydrocarbon or an oil such as epoxidized soy bean oil, or vegetable oil. Substances such as glycerol were identified as less or not suitable. The preferred compounds of this invention, the avermectins and milbemycins, are highly non-volatile compounds and are thus not usable in the vaporization type of devices. In addition, the instant device has a completely different mode of operation from that of EP 90446. The instant device, utilizing a hydrophylic carrier, in a polymeric matrix is significantly different from the prior devices.

SUMMARY OF THE INVENTION

This invention is concerned with a drug delivery device with a prolonged duration of activity for the administration of medicines. The drug delivery device consists of a water-incompatible polymeric matrix with a plasticizer if needed and an avermectin or milbemycin drug which is active topically which is dissolved in a vehicle capable of absorbing water. As water is absorbed by the vehicle from the environment, the vehicle develops a progressive incompatibility with the polymer matrix and is slowly expelled, along with the drug dissolved therein, from the matrix. Thus, it is an object of this invention to describe the particular form of the drug delivery device, for example as a flea and tick collar for pets. It is a further object of this invention to describe additional uses for such a system, such as medical implants, suppositories, ruminal boli, and non-medical uses such as water treatment devices or room deodorizers. A still further object is to describe the polymers which form the matrix or substrate for the active compound. A still further object is to describe the vehicle which contains the active drug. Still further objects will become apparent from a reading of the following description.

DESCRIPTION OF THE INVENTION

This invention relates to the production of drug delivery devices manufactured from polymeric materials. The drug delivery device is designed to provide for the release of the active drug over a prolonged period of time. In one embodiment of the device the drug that is delivered by the device provides protection for the wearer of the device against parasites. The preferred drugs are those of the avermectin and milbemycin families of drugs which are active antiparasitic agents against internal and external parasites. With the avermectin and milbemycin compounds when administered topically, as is done with the instant drug delivery device, the external parasites are killed, but in addition, the compounds have systemic effect when administered topically and the instant drug delivery device is thus able to treat internal and external parasites.

The slow release delivery device of this invention provides for the active drug or other active agent to be dissolved in a water-compatible vehicle which is then intimately contained within a water incompatible polymeric matrix. Thus, the drug delivery device is seen to be composed of three basic components; (1) The polymeric matrix, (2) the vehicle and (3) the drug or other active agent. The essential characteristics of the components are:

(1) The polymeric matrix is a linear thermoplastic polymer with a low intrinsic water absorption capability. The polymeric matrix should also possess sufficient crystallinity or glassiness at ambient temperature to at least partially resist absorption of a plasticizing solvent, but which will imbibe sufficient amounts of such solvent at elevated temperatures to form a homogeneous, stable organogel when cooled to ambient temperature.

(2) The vehicle is a plasticizing solvent for the polymer matrix with a solubility parameter such that it is soluble in the polymer matrix at elevated temperatures and sufficiently compatible at ambient temperature such that a stable homogeneous organogel is formed. In addition, the vehicle should be one such that water has a moderate solubility therein and in which the drug component has sufficient solubility to provide a therapeutically useful delivery rate and dosage over the period of usage of the device.

(3) The third component in the active drug as beneficial agent. The drug which is soluble in the vehicle can be any active agent whose nature only depends upon the intended use of the device. In one major aspect of this invention, the device is used as a flea and tick collar for domestic animals. In such cases the active agent is a topically active antiectoparasitic agent. As will be more fully explained below, the instant device can be used in any environment where water is present, either as atmospheric water vapor or as ambient liquid water. Thus, the drug or active agent could be any substance administered topically

in the form of a collar or transdermal patch; or any drug or substance administered by a suppository, rectal or vaginal; or any drug or substance administered by a subcutaneous implant; or any drug or substance administered orally by a tablet, capsule or ruminal bolus.

The operation of the instant device is predicated on the balancing the relative incompatibilities of the polymer matrix against the vehicle containing the drug in the anhydrous and in the hydrated states. The anhydrous vehicle drug combination should be sufficiently compatible with the polymer matrix such that at elevated temperatures a homogeneous blend is formed which is stable at room temperature. However, the vehicle and drug combination in the hydrated state should be incompatible with the polymer matrix and as a consequence thereof will be expelled from the polymer matrix in the form of a liquid exudate by the process of syneresis. The process of absorbing water into the vehicle is a continuous one, and can be regulated by the selection of the individual vehicle, the rate of expulsion of the vehicle and the drug contained therein. Thus, the exudation at the beneficial agent can be designed to occur over a prolonged period of use. The specific duration of expulsion will vary depending on the use to which the device is put and can extend for a few days, to one year, or even longer.

If the solid polymer (preferably in the form of small particles) is mixed with the plasticizing solvent (with or without dissolved drug) at ambient temperature, a viscous, liquid suspension is formed, which can be cast into any desired shape. If this suspension is now heated to a temperature sufficiently high to fuse or soften the polymer particles, these particles rapidly imbibe the surrounding plasticizing solvent (or solution) and swell to form plastically deformable gel particles which coalesce to yield an essentially homogeneous organogel. On cooling, this gel increases in rigidity, but retains its integrity as a stable, substantially homogeneous, elastically compliant mass.

Polymers or resins suitable for plastisol formulation are those thermoplastics of relatively high fusion- or softening-temperature which exhibit crystallinity, or possess glassy domains which soften only at elevated temperature. Typical examples include poly(vinyl chloride) and its copolymers with vinyl acetate or vinylidene dichloride; natural latex rubbers; polyethylene (both high-and low-density); isotactic polypropylene; poly(styrene, butadiene) block copolymers marketed under the trade name Kraton by Shell Chemical Co.; ethylene/vinyl acetate and ethylene/vinyl alcohol copolymers marketed by duPont under the trade names Elvax and Elvon; polyether- and polyester-based thermoplastic polyurethanes; and block copolymer glycol ether/terephthalate ester thermoplastic elastomers manufactured by duPont.

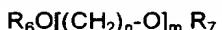
Plasticizing solvents suitable for plastisol formulation are well known to those in the art. They are generally high-boiling liquids of polarity close enough to that of the selected polymer to be capable of swelling or dissolving the polymer at elevated temperature (typically in excess of 140°C), but which will not significantly swell the polymer at ambient temperature. For polyvinyl chloride plastisols, such plasticizers include the esters of aliphatic and aromatic dibasic acids such as dibutyl sebacate and diethyl phthalate; for polyolefins and polymers such as Kraton, paraffinic and naphthenic hydrocarbons are often used.

For the purpose of the present invention, suitable plasticizing solvents must possess additional properties not normally required (and usually undesirable) for conventional plastisols. Firstly, the solvent must be capable of dissolving (and holding in solution at ambient temperature) reasonable amounts of the drug compound of interest; this means that the solvent must possess a solubility parameter not far different from that of the drug in question. The acceptable degree of solubility of the drug in the solvent is quite variable, depending on the potency of the drug, and the desired delivery rate and dosage. The preferred solubility range is probably not less than 5 parts, nor more than 150 parts per 100 parts plasticizing solvent.

Secondly, the plasticizing solvent must be of sufficient polarity (or high enough water solubility) to exhibit at least partial miscibility with water at ambient temperature. The solubility of water in the solvent must be sufficiently high to insure that, when water-saturated, the solvent will cease to be a plasticizing solvent for the polymer. While the water concentration at which solvent compatibility will be lost will vary from polymer to polymer, and solvent to solvent, it is expected that the solubility of water in the solvent (at ambient temperature) should be at least 1% by weight, and preferably greater than 10%; there is no upper limit on solubility.

At the same time, however, the solubility of the drug in the water-saturated solvent must be sufficiently high to assure that precipitation of drug from solution (at ambient temperature) will not occur to any significant extent. The choice of solvent will thus depend not only upon the polymer used, but also upon the water- and organic-solvent solubility of the drug to be incorporated. For PVC-based plastisols, the plasticizing solvents of choice are the alkoxylated polyethylene- or polypropylene glycol ethers (the Dowanols of Dow Chemical); poly(propylene) glycol; block-copolymer polyethylene glycol/polypropylene glycols (BASF-Wyandotte's Pluronics); and the ethoxylated alkylphenols (the Tritons of Rohm and Haas). The ethoxylated fatty acid esters of sorbitan (Tweens and Spans of ICI America) are also candidates. In those instances where the drug- and water-solubility in an otherwise suitable plasticizing solvent are inadequately high, mixtures of two or more such solvents, each of which alone may provide adequate drug- or water-solubility, may be useful.

The preferred vehicle or plasticizing solvent has the following formula:



where R_6 and R_7 are independently hydrogen, alkyl of from 1 to 12 carbon atoms in either a straight, branched or cyclic configuration, phenyl or alkanoyl of from 1 to 6 carbon atoms in either a straight or branched configuration;

n is 1 to 5; and

m is 1 to 10.

More preferred vehicles are realized in the above formula where R_6 and R_7 are hydrogen, alkyl of from 1 to 6 carbon atoms or phenyl;

n is 2 or 3; and

m is 2, 3 or 4.

The most preferred vehicles are realized in the above formula when R_6 is butyl, n is 2, m is 2 and R_7 is hydrogen; and when R_6 is methyl, n is 3, m is 2 and R_7 is hydrogen. The first compound is 2-(2-butoxy ethoxy) ethanol or diethylene glycol n-butyl ether which is also identified as Dowanol DB®. The second compound is (2-methoxy-methyl)ethoxy propanol or dipropylene glycol methyl ether which is also identified as Dowanol DPM®. Dowanol DB® and Dowanol DPM® are available from the Dow Chemical Co. of Midland Michigan, USA.

A plastisol formulated from the above three components, when fused at elevated temperature and transformed into an organogel, will consist of a three-dimensional polymer matrix, the interstices of which are filled with a solution of drug in the plasticizing solvent. For conventional organogels (as are used for plasticized PVC products) the volume fraction of plasticizing solvent in the gel is typically in the range of 0.3 to 0.5. For the purpose of this invention, the volume fraction of solvent solution in the gel can be much greater than this, and preferably may be as high as 0.9. The consequences of increasing the volume fraction of plasticizing solvent are to reduce the mechanical strength of the gel, and its stability on aging. These limitations can, however, be minimized by using a polymer of high molecular weight or by mechanically reinforcing the device with a strengthening cover or a mesh reinforcement. Most conventional plastisol PVC resins have molecular weights in the range of 8000 to 300,000 daltons; for the present invention, PVC with higher molecular weights up to 3 million, preferably from 50,000 to 1 million, may be used.

So long as an organogel of the subject invention is kept out of contact with moisture from any source the structure will be stable, and neither plasticizing solvent nor drug will escape from the mass during the normal lifetime of the device (if neither are volatile under these conditions). When, however, such an organogel is exposed to water, or to humid air, a series of events takes place leading to controlled, slow release of drug from the structure; these, in sequence, are as follows:

1. Water molecules migrate into the gel to form a solution of water in the plasticizing solvent; the gel gains weight and swells slightly during this process, but so long as the water content remains low enough to maintain compatibility of the solvent with the polymer, no other changes occur within the gel.

2. As the water content of the plasticizing solvent rises, a water concentration is reached at which the solvent becomes incompatible with the polymer. At that time, the polymer tries to precipitate from the solution, but because it is immobilized in a three-dimensional matrix, this matrix commences to collapse, forming microscopic droplets of (polymer-free) liquid within the gel matrix. The stresses created by the collapsing polymer matrix promote growth and coalescence of these droplets. The elastic stresses in the collapsing polymer network compress the liquid in the pores, and cause its expulsion from the gel at the gel surfaces. This phenomenon, usually referred to as "syneresis" or, "sweating", is a characteristic of unstable gel systems, and is well-documented in the scientific literature.

3. As water is continually imbibed, the syneresing gel continues to shrink and consolidate, expelling the drug-bearing, water absorbed, solvent mixture. As shrinkage proceeds, both the elastic stresses in the network are relieved, and the pore size in the now-microporous matrix decreases. This results in a decline in the rate of expulsion of liquid from the matrix, until finally - when the stresses become insignificant - syneresis ceases. However, in one embodiment of this invention, the operation of the device has been observed to continue in a constant fashion releasing active agent for a period exceeding 6 months, and durations of up to one year are possible.

In order to assist in the formation of devices such as pet flea and tick collars and to provide additional control in the texture, hardness, flexibility and duration of operation of the device, it may be advantageous to provide, in addition to the plasticizing solvent or vehicle, a plasticizer which is compatible with the solid polymeric macromolecular substance. It should be noted that the vehicle itself can also function as a plasticizer. The plasticizer should be at least partially compatible with the plasticizing solvent and, at least partially compatible with the polymer matrix. The presence of the plasticizer and the amount of plasticizer used can be used to regulate the rate of exudation of the plasticizing solvent and drug mixture as well as the physical properties

of the device. Examples of such primary plasticizers are hydrocarbon phthalates (for example dioctyl phthalate, diphenyl phthalate, dicyclohexyl phthalate, dimethyl phthalate and dihexyl phthalate); hydrocarbon sebacates (for example dipentyl sebacate, n-butyl benzyl sebacate and dibenzyl sebacate); and hydrocarbon adipates (for example dioctyl adipate, dicapryl adipate, di-isobutyl adipate and dinonyl adipate). Other compatible plasticizers are, for example, hydrogenated polyphenols; alkylated aromatic hydrocarbons; and polyester plasticizers, for example polyesters of polyols, such as hexanediol, and poly(carboxylic acids), such as sebacic or adipic acid, having molecular weights of about 2000.

Other materials (for example dyes, pigments, attractants, other biocides, lubricants, fillers, anti-oxidants and ultraviolet stabilizers) may be included in the material. For example, it has been found that the stability of the drug can be extended if a stabilizing amount, preferably 0.1% w to 10% w, of calcium stearate is included in the material. Other stabilizers that may be employed are, for example, bisphenolic and biphenolic stabilizers (for example bis-(3,5-di-tert.butyl-4-hydroxyphenyl)-methane; bis-(2-hydroxy-3-tert.buty-5-methylphenyl)-methane and 3,3',5,5'-tetra-tert.butyl-4,4'-dihydroxy biphenyl); naphthols (for example beta-naphthol) and benzyl alcohols (for instance 3,5-di-tert.butyl-4-hydroxybenzyl alcohol; 3,5-di-isopropyl-4-hydroxy-benzyl alcohol and 3-methyl-5-tert.butyl-4-hydroxy-benzyl alcohol).

Generally, the drug delivery device is composed of from 10 to 98% of the polymer and from 0 to 70% of the plasticizer, although these ratios may vary widely depending upon the particular nature of the polymer and plasticizer. The vehicle is present in the formulation at from 0.1 to 75% and the drug is present at from 0.1 to 60% The stablizer, if used, is present at from 0.1 to 10%. (all percentages are by weight).

Preferably the drug formulation contains from 30 to 70% of the polymer, from 0 to 60% of the plasticizer, from 5 to 50% of the vehicle and from 1 to 50% of the drug.

Most preferably the drug formulation contains from 35 to 60% of the polymer, from 0 to 30% of the plasticizer, from 10 to 45% of the vehicle and from 5 to 40% of the drug.

The instant devices, when used as flea and tick collars are designed to provide for a constant release of drug for a period of at least 6 months and preferably 12 months or even longer. The release rate of the collar will vary considerably depending upon the activity of the particular drug, the nature and the carrier and polymer matrix and the planned duration of the device. These variations can be readily determined by one skilled in the art. Of course, by varying the vehicle, the polymer and the plasticizer, different rates of release of the drug can be achieved.

The components of the instant drug delivery device are mixed and the devices are formed using techniques known to those skilled in polyemer manufacture. The devices are formed by combining the ingredients and heating the mixture to a temperature of from 100 to 200°C, preferably from 125 to 160°C, and more preferably from 135 to 160°C, or until a uniform melt is formed whereupon the melted mixture is shaped into the desired articles by the usual technique of casting, extrusion, injection molding and the like. Alternatively, the polymer and the plasticizer can be combined and heated to a melt and the drug and vehicle added thereto, either separately or with the drug predissolved in the vehicle. Since the components of the instant device may be somewhat volatile, depending on the individual plasticizing solvent, plasticizer or polymer selected, it is often advantageous to form the desired objects in a presurized mold. Pressure is not needed to form the objects themselves, however, only to prevent the loss of volatile components. Thus, the objected themselves need not be pressurized but only the mold in which the objects are formed. Pressures of from 1,000 to 10,000 psi (700,000 to 7,000,000 kg/m²) on the mold are preferred with pressures of 4,000 to 10,000 psi (2,800,000 to 7,000,000 kg/m²) more preferred.

The preferred form of the instant invention is as a flea and tick collar for household pets used as dogs and cats. In such a form the polymeric matrix is molded in the form of an elongated strip of which is 10 to 50 times longer than it is wide. In one embodiment of the invention, the collar is made in a single cross sectional area and shape and of a length which will fit the largest animals contemplated for the use of the collar and the dose for smaller animals is reduced by cutting off the length of the collar in excess of that needed to encircle the neck of the smaller animal.

Since the collars are intended for prolonged durations of use, the collars should be securely fastened to the animal about its neck in such a manner as to prevent its being removed by the normal activities of the animal such as scratching in the area of the collar or the presence of the animal in wooded or overgrown areas. To secure the collar to the animal the collar may be manufactured with a permanently attached buckle, clasp, snap or other attachment means.

The instant device operates by the absorbtion of water from the environment followed by the synergistic extrusion of drug-containing carrier from the device. When securely affixed about the neck of the animal, the environment, being in close proximity to the skin and fur of the animal, is in an environment which readily provides the atmospheric water vapor necessary for the operation of the device. However, when the synergistic extrusion occurs, it does so from all surfaces of the collar and, under certain circumstances the extruded drug-

containing liquid may not be deposited on the fur and skin of the animal where it can be effective in killing fleas and ticks on the animal, but the liquid may be deposited elsewhere by the animals activities which may involve rubbing its neck on environmental surfaces, such as bushes, lawns, furniture, carpets, pet owners and the like. This not only reduces the efficiency of the collar but result in drug-containing liquid being deposited in areas where it is not intended to be used.

This can be minimized by partially encasing the collar in a cover which can be installed over from one to three of the elongated surfaces of the collar. The cover will be installed on the collar such like the cover is on the outside and the open surface is in contact with the fur of the animal where the moist environment will ensure the operation of the device, and the normal movements of the animal ensure that the extruded liquid is spread to the fur and skin of the animal.

While the cover will obviously reduce the rate of extrusion of the device since one or more surfaces normally used for extrusion are blocked, this can be overcome by making the collar wider with a larger surface area facing the fur of the animal, or by making the polymeric matrix thinner so that the internal resistance to the flow of the drug and carrier is minimized and the maximum amount of drug is released to the neck of the animal. Alternatively, the composition of the polymericmatrix and/or the hydrophylic carrier can be adjusted for a greater rate of flow.

The cover can be constricted so that it is firmly bonded to the collar to impart strength to the collar-cover system so that there will not be any damage to the system if the collar is scratched by the animal, caught on a branch or other object or abraded by rough objects such as tree bark and the like.

The cover can be constructed in the form of a fiber backing which will impart strength to the collar but have minimal effect on the extrusion rate of the collar. The mesh can be either bonded to the surface or embedded within the collar. Alternatively the cover can be constructed to be completely bonded to at least the outside surface of the collar and optionally the edges of the collar can be similarly covered with a backing material which will seal the surfaces of the collar not directly in contact with the fur of the animal, impart strength to the system and also provide a degree of insulation to the collar. This will provide for a more narrow range of operating temperatures for the collar which would result in a more uniform and predictable rate of extrusion of drug from the collar.

These various aspects of the collar are shown in the accompanying drawings where Figure 1, parts A, B and C show the collar without the installation of fastening means in top, side and edge views.

Figure 2 shows an embodiment of the collar in a top view with a mesh backing (2) to impart strength to the polymeric matrix (1).

Figure 3A shows an embodiment of the collar in enlarged cross section with the polymeric matrix (1) bonded to a cover (3) which is attached only to the outside surface of the collar. Figure 3B shows another version of the collar with the cover (3) attached to the outside and edges of the polymeric matrix (1).

As noted above, the instant drug delivery device can be used in a variety of forms to deliver a beneficial agent or other active agent to a variety of bodily system. Thus, the selection of the particular beneficial agent to be place in the device used need not be limited.

The expression, "beneficial agent" as used herein denoted any benificial agent or compound that can be delivered by the instant device to produce a beneficial and useful result. The term, "beneficial agent" includes biocide, parasiticide, fungicide, larvicide, flukicide, medicine or drug, nutrient, vitamin, food supplement, mineral, anthelmintic, anti-infestation, growth promontant, ionophore, and other agents that benefit the environment of use. In the specification and the accompanying claims the term, "beneficial agent" includes any physiologically or pharmacologically active substances that produce a local or systemic effect in animals, including warm-blooded mammals; humans and primates; household, sport, farm and zoo animals. The term, "physiologically" as used herein denotes the administration of a drug to produce normal levels and functions. The term, "pharmacologically" denotes variations in response to an amount of drug administered to the host. Stedman's Medical Dictionary, 1966, published by Williams and Wilkins, Baltimore, Md. The beneficially active drugs that can be delivered by the instant device include inorganic and organic drugs, such as drugs that act on the central nervous system, depressants, hypnotics, sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants, antiparkinson agents, analgesic, anti-inflammatory, anesthetics, muscle contractants, antimicrobials, antimalarials, hormonal agents contraceptives, diuretics, sympathomimetics antiparasitics, neoplastics, hypoglycemics, ophthalmics, electrolytes, cardiovascular drugs and the like.

Exemplary drugs that can be delivered by the delivery device are prochlorperazine edisylate, ferrous sulfate, aminocaproic acid, potassium chloride, mecamylamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, benzphetamine hydrochloride, isoproterenol sulfate, methamphetamine hydrochloride, phenmetrazine hydrochloride, bethanechol chloride, methacholine chloride, pilocarpine hydrochloride, atropine sulfate, methascopolamine bromide, isopropamide iodide, tridehexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, oxprenolol hydrochloride, metoprolol tartrate, cimetidine hydrochloride,

diphenidol, meclizine hydrochloride, prochlorperazine maleate, phenoxybenzamine, thiethylperazine maleate, anisindone, diphenadione, erythrityl tetranitrate, dizoxin, isofurophate, reserpine, acetazolamide, methazolamide, bendroflumethiazide, chlorpropamide, tolazamide, chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, progestins, estrogenic steriods, progestational steriods, corticosteriods, hydrocortisone, 17 β -estradiol, ethenyl estradiol, ethynodiol dihydrogesterone, prednisolone, hydrocorticosterone acetate, triamcinolone, methyltestosterone, 17 β -hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel, norethindrone, norethisterone, progeterone, norgesterone, norethynodrel, and the like.

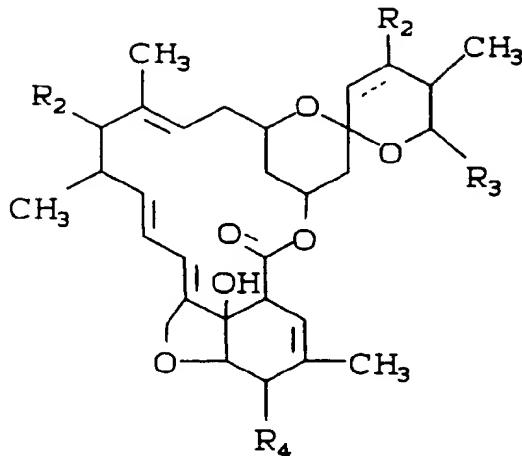
Examples of other beneficial drugs that can be delivered by the delivery device include aspirin, indometacin, naproxen, fenoprofen, sulindac, diclofenac, indoprofen, nitroglycerin, propanolol, valproate, timolol, atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine, reserpine, methyl-dopa, dihydroxyphenylalanine, praloxoxyethyl ester of α -methyldopa hydrochloride, theophylline, calcium gluconate, ferrous lactate, vincamine, diazepam, phenoxybenzamine, blocking agents, and the like. The beneficial drugs are known to the art in *Pharmaceutical Sciences*, by Remington, 14th Ed., 1979, published by Mack Publishing Co., Easton, Pa.; *The Drug; The Nurse, The Patient, Including Current Drug Handbook, 1974-1976*, by Falconer et al, published by Sunder Co., Philadelphia, Pa., and *Medical Chemistry*, 3rd Ed, Vol. 1 & 2, by Burger, published by Wiley-Interscience, new York.

Representative of beneficial medicaments that can be delivered to warm-blooded animals, including ruminants, using the delivery system of this invention, include anthelmintics such as mebendazole, levamisole, albendazole, cambendazole, fenbendazole, parbendazole, oxfendazole, oxybendazole, thiabendazole, ti-chlorfon, praziquantel, morantel and parantel, and the like; antiparasitic agents such as avermectin and ivermectin, as disclosed in U.S. Pat. Nos. 4,310,519, 4,199,569 and 4,389,397, all assigned to Merck & Co., and in *Science*, Vol. 221, pp 823-828, 1983, wherein said ivermectin antiparasitic drugs are disclosed as useful for aiding in controlling commonly occurring infestations in animals, such as roundworms, lung worms, and the like, and said ivermectin also being useful for the management of insect infestations such as grub, lice, mange mite, and the like; antimicrobial agents such as chlortetracycline, oxytetracycline, tetracycline, streptomycin, gentamicin, dihydrostreptomycin, bacitracins, erythromycin, ampicillins, penicillins, cephalosporins, and the like; sulfa drugs such as sulfamethazine, sulfathiazole, and the like; growth stimulants such as Monesin® sodium and Elfazepam®; defleating agents such as dexamethazone and flumethazone; rumen fermentation manipulators and ionophores such as lasalocid; virginiamycin, salinomycin and ronnel; minerals and mineral salts; anti-bloat agents such as organopoly siloxanes; hormone growth supplements such as stilbestrol; vitamins; anti-enteritis agents such as furazolidone; growth efficiency factors such as β -agonists, clenbuterol, nutritional supplements such as lysine monohydrochloride, methionine, magnesium carbonate, ferrous and ferric compounds, copper oxide, cobalt sulphate, sodium selenite, potassium iodide, zinc oxide and manganese sulphate, and the like, and chemical markers such as chromic oxide, salts of ytterbium and erbium.

The agents or drugs can be in various forms, such as uncharged molecules, molecular complexes, pharmacologically acceptable salts such as hydrochlorides, hydro-bromide, sulfate laurylate, palmitate, phosphate, nitrate, borate, acetate, maleate, tartrate, oleate, salicylate, and the like. For acid drugs, salts of metals, amines, or organic cations, for example, quaternary ammonium can be used. Derivatives of drugs such as esters, ethers, amides, and the like, can be used. Drug that are water insoluble can be in form that is converted by enzymes, hydrolyzed by body pH or other metabolic processes, to the original biologically active form.

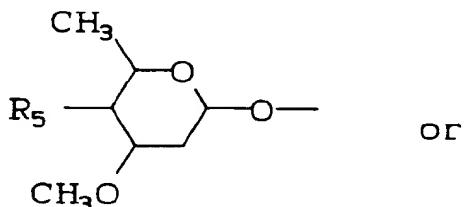
The term, "animal" is used herein generically denotes any animal such as man, camel,; cattle,; dog, cat,; goat,; sheep, swine,; deer,; bison,; giraffe,; horse, and elephant.

The preferred beneficial agent or drug to be used in the instant drug delivery device is an active antiparasitic compound or compounds selected from the following generic formula which includes compounds from the avermectin and milbemycin families of compounds.

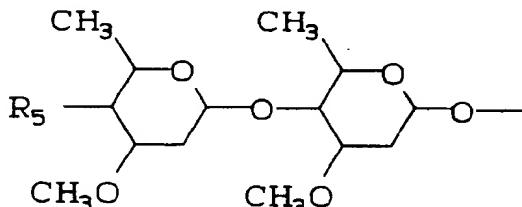


where R₁ can be H, OH, C₁-C₈-alkoxy, poly C₁-C₈ alkoxy,

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where the broken line indicates a single or a double bond;

R₂ is H, OH, -O-C₁-C₈-alkanoyl, C₁-C₈-alkoxy, oxime or substituted oxime where the substituent is C₁-C₈-alkyl, and R₂ is present only when said broken line indicates a single bond;

45

R₃ is C₁-C₈-alkyl, C₂-C₈-alkenyl, C₃-C₈ cycloalkyl or heterocyclic;

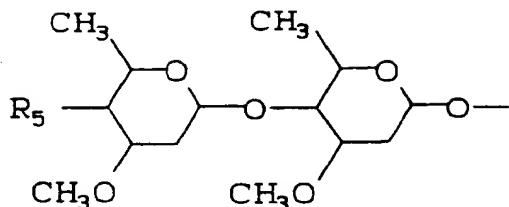
R₄ is OH, -O-C₁-C₈-alkanoyl, C₁-C₈-alkoxy, oxime or substituted oxime where the substituent is C₁-C₈-alkyl;

R₅ is OH, -O-C₁-C₈-alkanoyl, =O, amino, substituted amino where the substituents are C₁-C₈-alkyl, C₁-C₈-dialkyl or C₁-C₈-alkanoyl, O-phosphate or O-hemisuccinate.

50

Preferred compounds for use in the instant dosage delivery device are realized in the above formula where R₁ is hydrogen, poly C₁-C₈-alkoxy or

55



10 with the broken line indicating a single bond;

R_2 is hydrogen;

R_3 is $C_1\text{-}C_8$ -alkyl, $C_2\text{-}C_8$ -alkenyl or $C_3\text{-}C_8$ -cycloalkyl;

R_4 is OH, $C_1\text{-}C_8$ -alkoxy or oxime; and

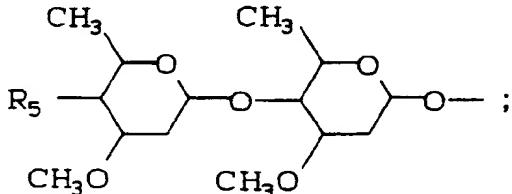
15 R_5 is OH, amino, or substituted amino where the substituent is $C_1\text{-}C_8$ -alkyl, di- $C_1\text{-}C_8$ -alkyl, or $C_1\text{-}C_8$ -al-

kenyl.

Additional preferred compounds are realized where:

R_1 is hydrogen, poly $C_1\text{-}C_3$ -alkoxy, or

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R_2 is hydrogen and a broken line indicates a single bond;

R_3 is $C_3\text{-}C_4$ -alkyl, $C_3\text{-}C_6$ -alkenyl or $C_5\text{-}C_6$ -cycloalkyl;

30 R_4 is hydroxy, $C_1\text{-}C_3$ -alkoxy or oxime; and

R_5 is OH, amino or substituted amino where the substituent is $C_1\text{-}C_3$ -alkyl, di- $C_1\text{-}C_3$ -alkyl or $C_2\text{-}C_3$ -al-

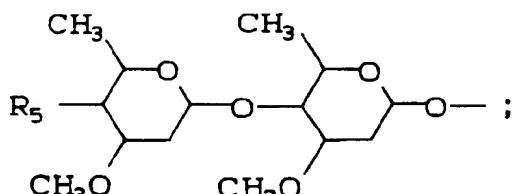
kanoyl or $C_1\text{-}C_3$ -alkyl- $C_2\text{-}C_3$ -alkanoyl.

Still further preferred compounds are realized when R_1 is hydrogen, $C_1\text{-}C_2$ alkoxy- $C_1\text{-}C_2$ -alkoxy- $C_1\text{-}C_2$ -al-

koxy or

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R_2 is hydrogen and the broken line indicates a single bond;

R_3 is isopropyl, sec-butyl cyclopentyl or cyclohexyl;

R_4 is hydroxy, methoxy or oxime; and

R_5 is OH, amino, N-methylamino, N,N-dimethylamino N-acetyl amino or N-acetyl-N-methylamino.

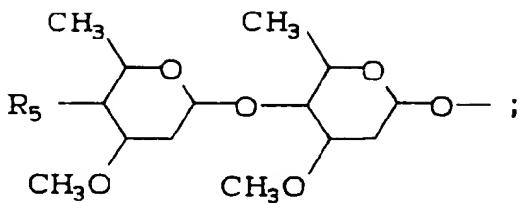
The most preferred compounds are realized when

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(1)

R_1 is

55



10 R₂ is hydrogen and its broken line indicates a single bond;
 R₃ is isopropyl or sec-butyl; and
 R₄ is hydroxy.

15 (2) R₁ is methoxy-ethoxy-methoxy;
 R₂ is hydrogen and the broken line indicates a single bond;
 R₃ is isopropyl or sec-butyl; and
 R₄ is hydroxy.

20 (3) R₁ is methoxy-methoxy;
 R₂ is hydrogen and broken line indicates a single bond;
 R₃ is isopropyl or sec-butyl; and
 R₄ is hydroxy.

The following examples are provided in order that the invention may be more fully understood. They are not to be construed as limitative of the invention.

25 EXAMPLE 1

A polymeric matrix flea collar containing Compound 1, 22,23-dihydro avermectin B1a/B1b (ivermectin) in a PVC polymeric matrix is prepared from the following materials in the following proportions by weight:

30

Ingredient	Proportion
Polyvinyl chloride powder (GEON 121)	55
Diethyl adipate	8
Calcium stearate	2
Dowanol DB	20
Ivermectin	15

40 The Dowanol DB and the ivermectin are combined and stirred until solution is achieved. Then the remainder of the materials are added and thoroughly mixed. The liquid mixture is degassed in a vacuum at 25°C for 1 hour. The liquid is then poured into a metal pressurized mold at 140°C and the mold temperature maintained at 140°C and the pressure maintained on the mold at 6,000 psi (4,200,000 kg/m²) for 20 or 30 minutes. The mold is then opened and the solid polymeric matrix flea collar removed.

45 A sample of the flea collar typically prepared according to the above example in in vitro test was developed as a surrogate to the application of a collar to an animal to determine the release rate of the drug from the collar. After the collar was prepared with ivermectin as described above, it is stored in a 50% constant humidity chamber to simulate an environment close to the skin of an animal. Once a day the collar is removed and wiped once with a soft cloth and weighed.

50 Following such a procedure the collars in the simulated test lost an average 13 to 14 mg per day of the drug plus vehicle for a total area of 122 cm² of the collar and the release rate was seen to be very close to zero-order, that its the collar lost about the same amount each day.

55 The cumulative weight loss of collars prepared as described above and tested using the surrogate testing procedure is found in the graph of Figure 4 where the Y-axis plots the cumulative weight loss of the collar and the X-axis plots the duration of the test in days. The dimension of the polymeric matrix flea collar is 25.4 x 132 x 4mm and weighed approximately 15g at the start of the test. The solid triangles show the cumulative weight loss for sample heated for 20 minutes and the solid squares show the cumulative weight loss for the

sample heated for 30 minutes. The numbers in parentheses are the weights of the samples at the start of the test.

EXAMPLE 2

5 A polymeric matrix flea collar containing Compound (2) above as the active ingredient (13-methoxy-ethoxy-methoxy-22,23-dihydro avermectin B1a/B1b) is prepared from the following materials in the following proportions:

	Ingredient	Proportion
10	Polyvinyl chloride powder (GEON 121)	50
	Diethyl adipate	12
15	Calcium stearate	2
	Dowanol DB	24
	Compound (2)	14

20 Compound 2 is dissolved in the Dowanol DB and the remaining ingredients are combined and mixed thoroughly. The liquid mixture is degassed in vacuo at room temperature for 20 minutes and poured into a metal mold at 140°C. The mold is pressurized to 6,000 psi (4,200,000 kg/m²) and the mold temperature of 140°C maintained for 20 minutes. The mold is opened and the solid collar removed and tested in the surrogate testing procedure described in Example 1. The results of the test are shown for two collars prepared by this procedure in the graph of Figure 5. The release is seen to be substantially linear for a period in excess of 250 days. The open squares and open triangles show the cumulative weight loss for two samples prepared as above (140 C mold temperature and heating time for 20 minutes followed by the weights of the samples at the start of the test.

30 EXAMPLE 3

A polymeric matrix flea collar containing Compound (2) as the active ingredient is prepared from the following materials in the following proportions.

	Ingredient	Proportion
35	Polyvinyl chloride powder (GEON 121)	52
	Calcium stearate	1.5
40	Butylated hydroxy toluene (BHT) (antioxidant)	0.5
	Dowanol DB	32.
	Compound 2	14.

45 Compound 2 is dissolved in the Dowanol DB and the rest of the materials added thereto and mixed thoroughly. The liquid mixture is degassed in vacuo at room temperature and poured into a 140°C mold at 6,000 psi (4,200,000 kg/m²) on the mold for 20 minutes as in Example 1 and 2. Several samples of the collar were prepared and some of them were sealed into air and water impervious aluminum lined pouches. The samples were tested in the procedures described in Example 1 with a first collar placed under test on day 0 with the remainder of the samples kept under seal. One sealed package was opened and the collar placed under test on day 18 and a second collar opened and placed under test on day 60. The result of the tests are shown in the graph in Figure 6. The open squares show the cumulative weight loss for the first sample; the open triangles show the cumulative weight loss for the sample unsealed on day 18; and the solid triangles show the cumulative weight loss for the sample unsealed on day 60. The test results show that the samples do not lose any weight until they are exposed to the 50% humidity test conditions since the sealed samples did not gain or lose any weight until they were unsealed. In addition, the samples all showed substantially linear cumulative weight loss with approximately the same slope.

Claims

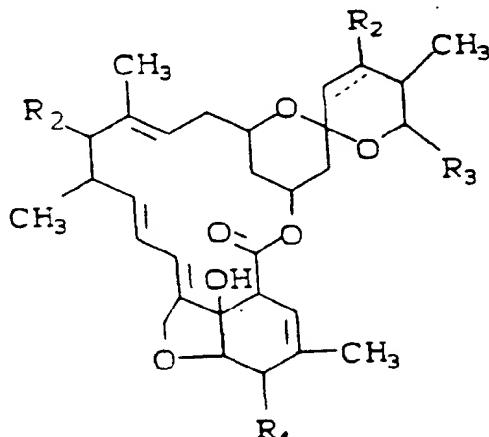
1. A drug delivery device compounded of a polymeric matrix, a vehicle and a drug such that:
 - a) the polymeric matrix is a linear thermoplastic polymer with a low intrinsic water absorption capability; and where the polymeric matrix is at ambient temperature at least partially resistant to absorption of the vehicle but which will imbibe sufficient quantities of the vehicle at elevated temperature to form a stable homogeneous organogel when cooled to ambient temperature.
 - b) the vehicle is a plasticizing solvent for the polymeric matrix which is fusible in the polymeric matrix at elevated temperature and wherein water is moderately soluble in the vehicle; and
 - c) the drug is soluble in the vehicle.
2. The drug delivery device of Claim 1 where the polymeric matrix is poly(vinyl chloride) and its copolymers with vinyl acetate or vinylidene dichloride, high and low density polyethylene, isotactic polypropylene, styrene-butadiene block copolymers, ethylene/vinyl acetate and ethylene/vinyl alcohol copolymers, polyether and polyester - based thermoplastic polyurethane or block copolymer glycol ether/terphthalate ester thermoplastic elastomers.
3. The drug delivery device of Claim 2 where the polymer is poly(vinyl chloride).
4. The drug delivery device of Claim 1 which also includes a plasticizer.
5. The drug delivery device of Claim 4 where the plasticizer is a hydrocarbon phthalate, a hydrocarbon sebacate, a hydrocarbon adipate, a hydrogenated polyphenol, alkylated aromatic hydrocarbon, polyester or poly(carboxylic acids).
6. The drug delivery of Claim 1 which is a flea and tick collar for domestic animals.
7. The drug delivery device of Claim 1 where the drug is an avermectin or a milbemycin.
8. The drug delivery device of Claim 7 where the drug has the structural formula:

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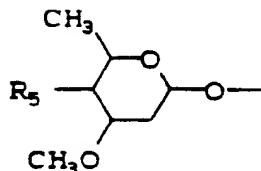
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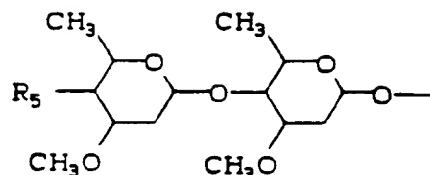
where R₁ can be H, OH, C₁-C₈-alkoxy, poly C₁-C₈ alkoxy,

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or



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where the broken line indicates a single or a double bond;

R_2 is H, OH, -O-C₁-C₈-alkanoyl, C₁-C₈, alkoxy, oxime or substituted oxime where the substituent is C₁-C₈-alkyl, and is present only when said broken line indicates a single bond;

R_3 is C₁-C₈-alkyl, C₂-C₈-alkenyl, C₃-C₈-cycloalkyl or heterocyclic;

15

R_4 is OH, O-C₁-C₈-alkanoyl, C₁-C₈-alkoxy, oxime or substituted oxime where the substituent is C₁-C₈-alkyl.

R_5 is OH, -O-C₁-C₈-alkanoyl, =O, amino, substituted amino where the substituents are C₁-C₈-alkyl, di-C₁-C₈-alkyl or C₁-C₈-alkanoyl, O-phosphate or O-hemisuccinate.

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9. The drug delivery device of Claim 4 which comprises from 10 to 98% of the polymeric macromolecule, from 0 to 70% of the plasticizer, from 0.1 to 75% of the vehicle and from 0.1 to 60% of the drug.

10. The slow-release drug delivery device of Claim 9 which comprises from 35 to 60% of the polymeric macromolecule, from 0 to 30% of the plasticizer, from 10 to 45% of the vehicle and from 5 to 40% of the drug.

25

11. A process for the preparation of a drug delivery device as claimed in claim 1, which comprises mixing the matrix-forming thermoplastic polymer with a solution of the drug in the plasticizing solvent at ambient temperature; heating the resulting suspension to a temperature sufficiently high to fuse or soften the thermoplastic polymer; and cooling the gel thereby obtained.

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Figure 1

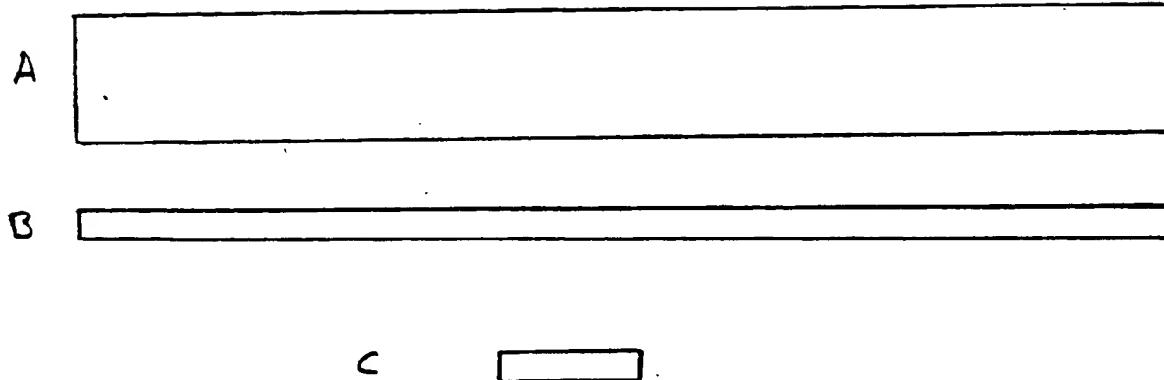


Figure 2

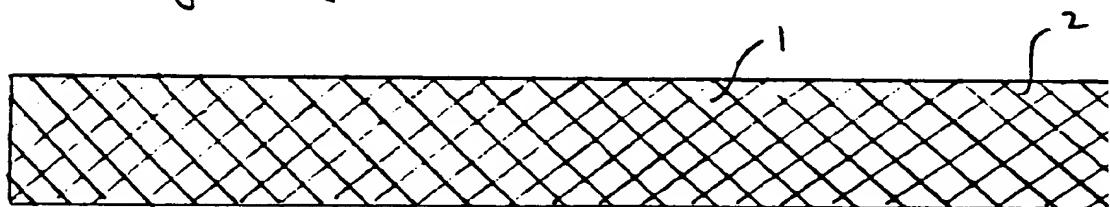


Figure 3

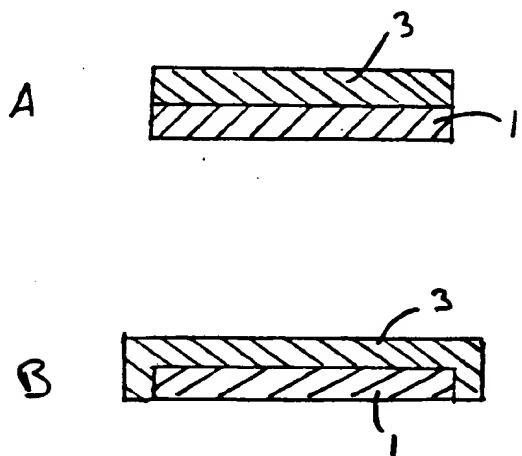


FIGURE 4
CUMULATIVE WEIGHT LOSS

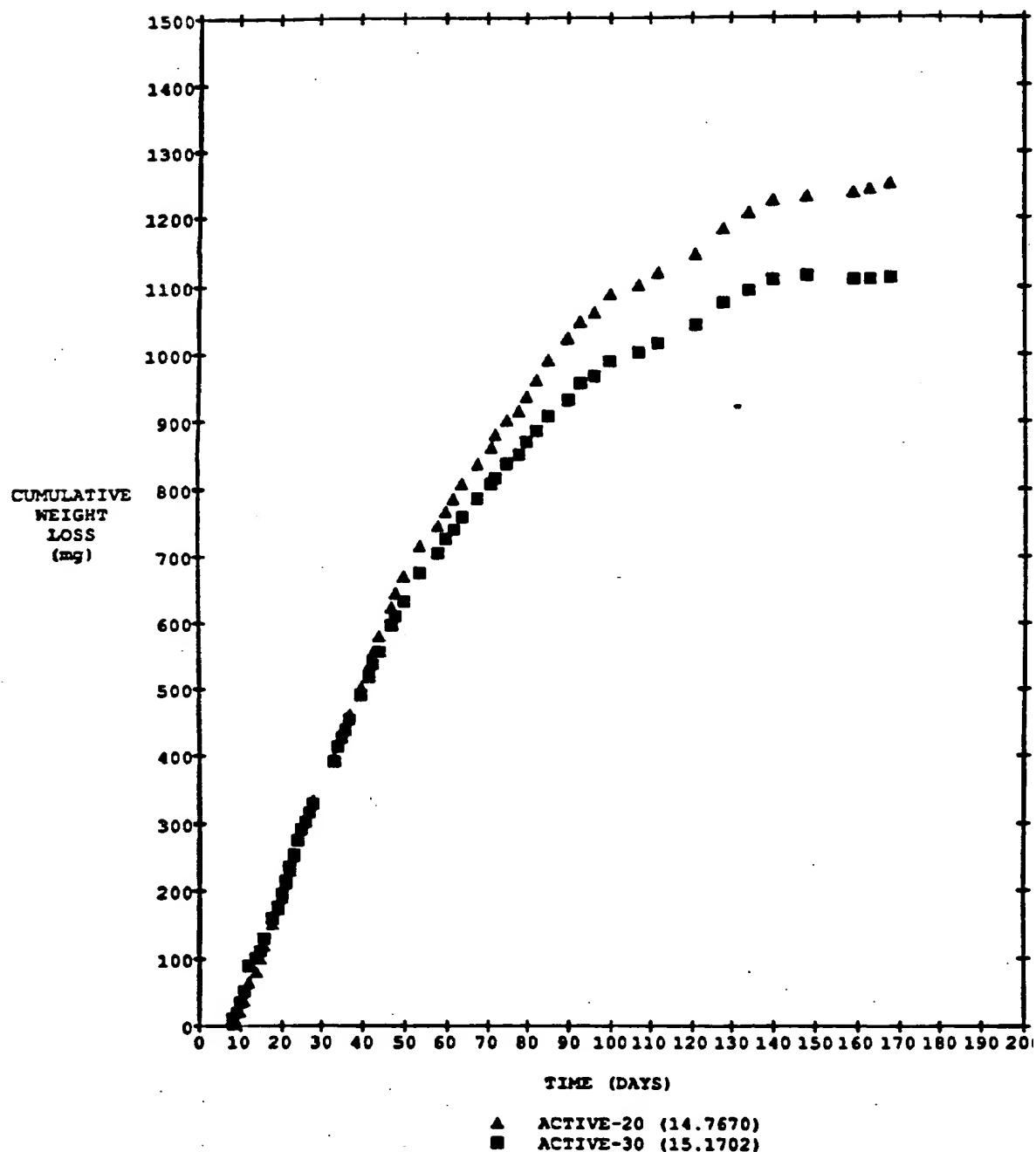


FIGURE 5
CUMULATIVE WEIGHT LOSS

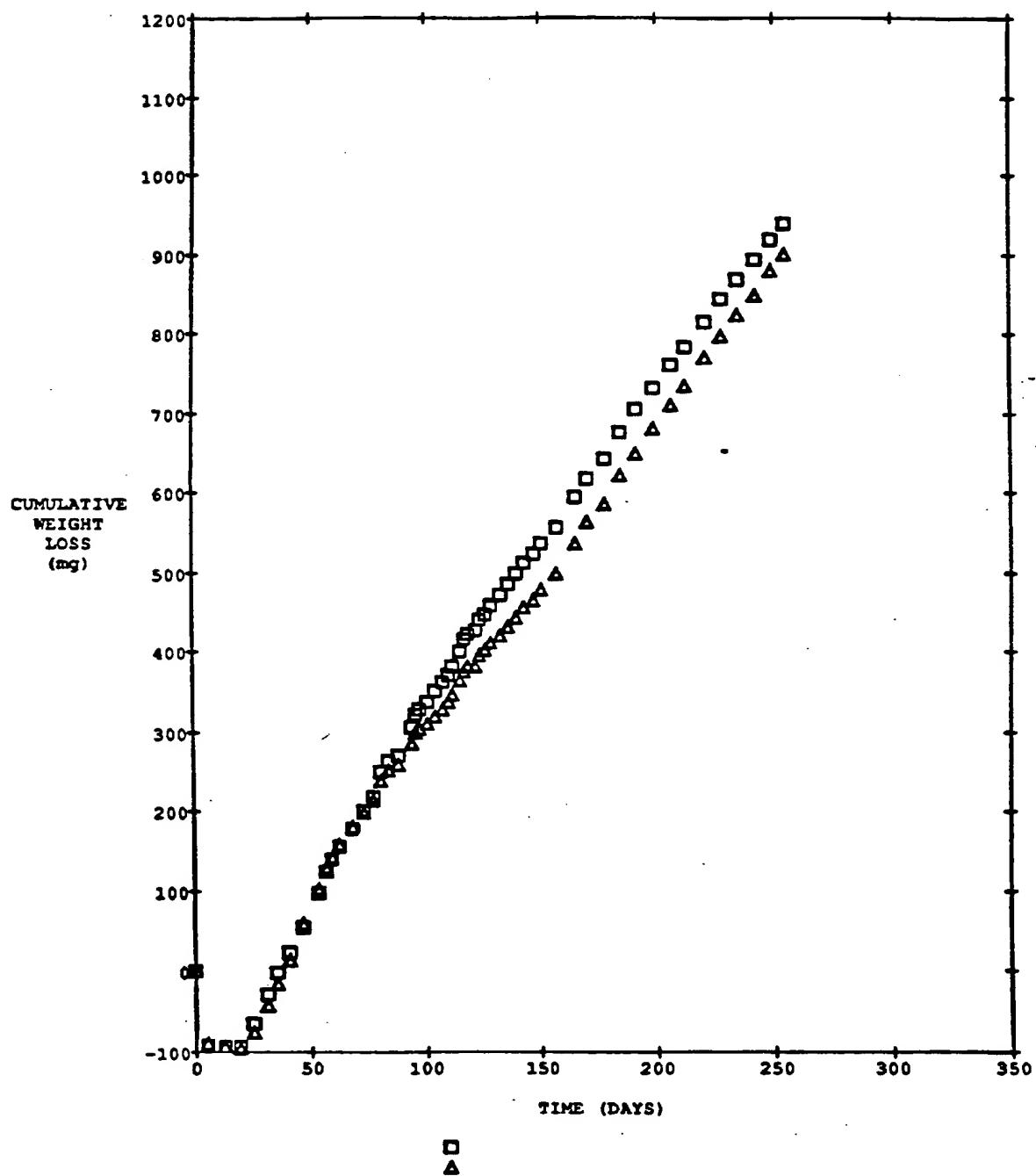
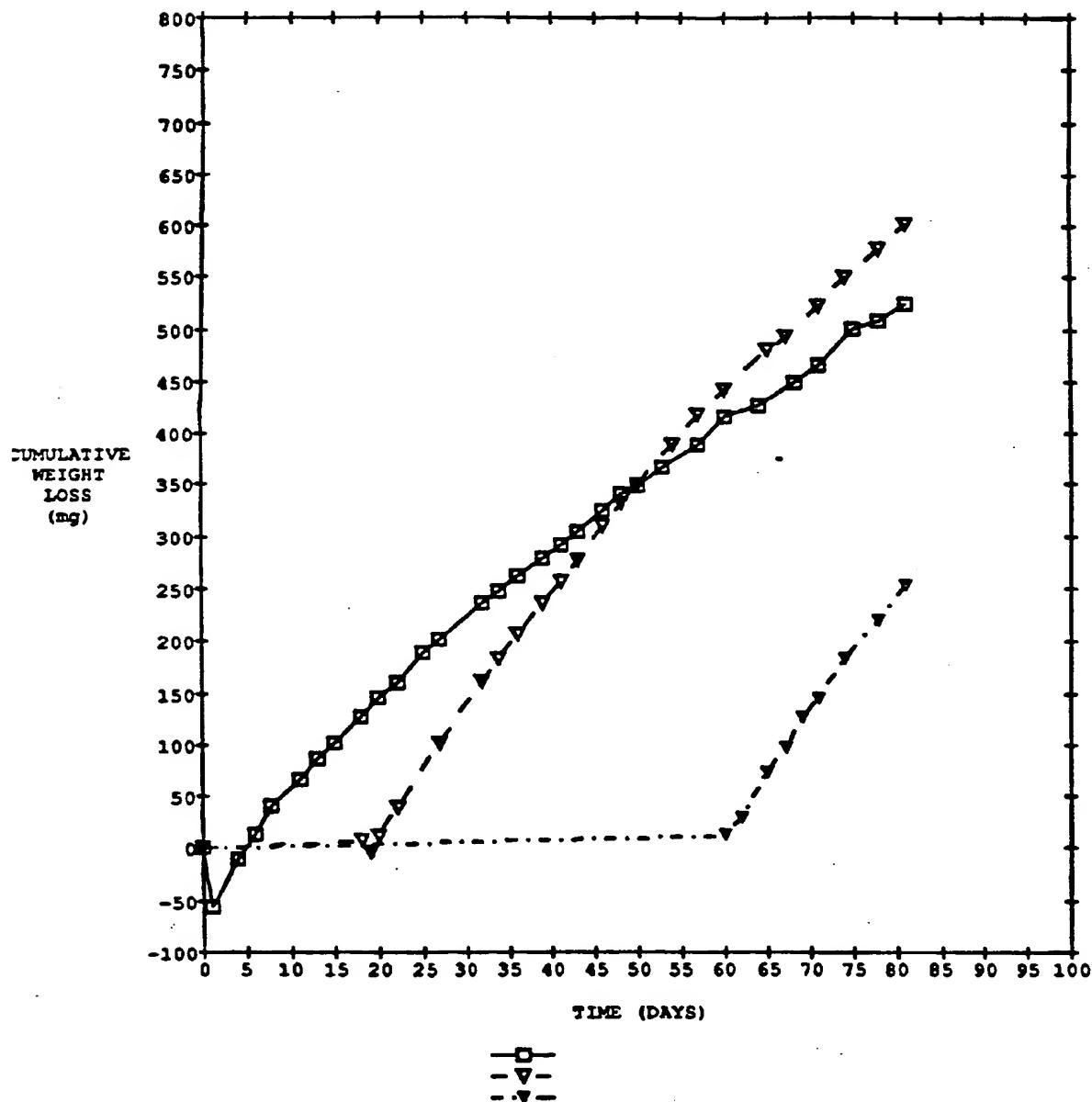


FIGURE 6
CUMULATIVE WEIGHT LOSS





European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 30 9346

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D, Y	EP-A-0 090 446 (SHELL) * claims * * page 3, line 32 - line 35 * * page 4, line 1 - line 25 * * page 5, line 1 - line 20 * * page 8, line 20 - line 34 * * page 11, line 1 - line 19 * --- 	1-11	A61K9/20 A01N25/10 A01N25/34
Y	EP-A-0 052 411 (ZOECON CORPORATION) * claims 1-6 * * page 2, line 22 - line 35 * * page 3, line 1 - line 32 * * example 3 * --- 	1-11	
Y	US-A-3 852 416 (L.M.GRUBB) * claims * * column 2, line 50 - line 55 * * column 3, line 3 - line 53 * --- 	1-11	
Y	US-A-4 764 382 (A.F.KYDONIEUS) * claims * * column 4, line 35 - line 58 * * column 5, line 14 - line 33 * * column 7, line 22 - line 34 * * column 7, line 63 - line 68 * --- 	1-11	
Y	FR-A-2 391 721 (ALZA) * claims 1-9 * * page 5, line 24 - line 34 * * page 6, line 3 - line 6 * * page 8, line 30 - line 35 * ----- 	1-11	A61K A01N
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	11 JANUARY 1993	SCARPONI U.	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone	T : theory or principle underlying the invention		
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A : technological background	D : document cited in the application		
O : non-written disclosure	L : document cited for other reasons		
P : intermediate document	& : member of the same patent family, corresponding document		

(19)



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(11) EP 0 537 998 B1

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A01N 25/34**

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(22) Date of filing: **14.10.1992**

(54) Controlled release drug delivery device comprising a polymer matrix and a plasticizer

Wirkstoffabgabevorrichtung mit gesteuerter Freigabe enthaltend eine Polymermatrix und einen Weichmacher

Dispositif d'administration de médicaments à libération contrôlée comprenant une matrice de polymère et un plastifiant

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: **15.10.1991 US 776913**

(43) Date of publication of application:
21.04.1993 Bulletin 1993/16

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(56) References cited:
EP-A- 0 052 411 **EP-A- 0 090 446**
FR-A- 2 391 721 **US-A- 3 852 416**
US-A- 4 764 382

EP 0 537 998 B1

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Description**BACKGROUND OF THE INVENTION**

5 The use of flea and tick collars is well known with most commercial versions of such devices being of the vaporization type where the active drug is slowly released from the polymeric collar in the form of a vapor. In European Patent Application 90446 a polymeric support material is combined with a plasticizer and a carrier for a pyrethroid contact pesticide, which may be volatile or non-volatile, where the carrier is incompatible with the polymer. The carrier is in the form of a chlorinated hydrocarbon or an oil such as epoxidized soy bean oil, or vegetable oil. Substances such as glycerol
10 were identified as less or not suitable. The preferred compounds of this invention, the avermectins and milbemycins, are highly non-volatile compounds and are thus not usable in the vaporization type of devices. In addition, the instant device has a completely different mode of operation from that of EP 90446. The instant device, utilizing a hydrophylic carrier, in a polymeric matrix is significantly different from the prior devices.

Further prior art is described in the following documents:

15 EP-A-0 052 411 describes pet collars comprising a solid resin, a plasticizer and the ectoparasiticide, phosmet, wherein the active ingredient is rendered odourless by being in a specified recrystallised form.

US-3,852,416 describes tick and flea collars comprising a solid, substantially non-volatile carbamate and a plasticized solid thermoplastic resin.

20 US-4,764,382 describes a drug delivery device comprising a polyvinyl chloride gel and a pharmacological agent dispersed therein. The gel is prepared from a polyvinyl resin, a primary plasticizer for the resin and an organic non-volatile gel forming additive.

FR-A-2,391,721 describes a drug delivery system comprising a thermoplastic copolyester, an active agent and, if necessary, a plasticizer.

25 None of these references describe a system of the present invention as claimed in claim 1, namely a device which comprises a polymer with a low intrinsic water absorption capability, which is compatible with a vehicle which is capable of dissolving water and where the initial state of compatibility changes to incompatibility upon dissolution of water in the vehicle. A drug which is dissolved in the vehicle is expelled by syneresis from the polymeric matrix when the vehicle becomes incompatible with the polymer.

SUMMARY OF THE INVENTION

30 This invention is concerned with a drug delivery device with a prolonged duration of activity for the administration of medicines. The drug delivery device consists of a water-incompatible polymeric matrix with a plasticizer if needed and an avermectin or milbemycin drug which is active topically which is dissolved in a vehicle capable of absorbing water. As water is absorbed by the vehicle from the environment, the vehicle develops a progressive incompatibility with the polymer matrix and is slowly expelled, along with the drug dissolved therein, from the matrix. Thus, it is an object of this invention to describe the particular form of the drug delivery device, for example as a flea and tick collar for pets. It is a further object of this invention to describe additional uses for such a system, such as medical implants, suppositories, ruminal bolus and non-medical uses such as water treatment devices or room deodorizers. A still further object is to describe the polymers which form the matrix or substrate for the active compound. A still further object is to describe the vehicle which contains the active drug. Still further objects will become apparent from a reading of the following description.

DESCRIPTION OF THE INVENTION

45 This invention relates to the production of drug delivery devices manufactured from polymeric materials. The drug delivery device is designed to provide for the release of the active drug over a prolonged period of time. In one embodiment of the device the drug that is delivered by the device provides protection for the wearer of the device against parasites. The preferred drugs are those of the avermectin and milbemycin families of drugs which are active antiparasitic agents against internal and external parasites. With the avermectin and milbemycin compounds when administered topically, as is done with the instant drug delivery device, the external parasites are killed, but in addition, the compounds have systemic effect when administered topically and the instant drug delivery device is thus able to treat internal and external parasites.

50 The slow release delivery device of this invention provides for the active drug or other active agent to be dissolved in a water-compatible vehicle which is then intimately contained within a water incompatible polymeric matrix. Thus, the drug delivery device is seen to be composed of three basic components; (1) The polymeric matrix, (2) the vehicle and (3) the drug or other active agent. The essential characteristics of the components are:

(1) The polymeric matrix is a linear thermoplastic polymer with a low intrinsic water absorption capability. The pol-

ymeric matrix should also possess sufficient crystallinity or glassiness at ambient temperature to at least partially resist absorption of a plasticizing solvent, but which will imbibe sufficient amounts of such solvent at elevated temperatures to form a homogeneous, stable organogel when cooled to ambient temperature.

(2) The vehicle is a plasticizing solvent for the polymer matrix with a solubility parameter such that it is soluble in the polymer matrix at elevated temperatures and sufficiently compatible at ambient temperature such that a stable homogeneous organogel is formed. In addition, the vehicle should be one such that water has a moderate solubility therein and in which the drug component has sufficient solubility to provide a therapeutically useful delivery rate and dosage over the period of usage of the device.

(3) The third component in the active drug as beneficial agent. The drug which is soluble in the vehicle can be any active agent whose nature only depends upon the intended use of the device. In one major aspect of this invention, the device is used as a flea and tick collar for domestic animals. In such cases the active agent is a topically active antiectoparasitic agent. As will be more fully explained below, the instant device can be used in any environment where water is present, either as atmospheric water vapor or as ambient liquid water. Thus, the drug or active agent could be any substance administered topically in the form of a collar or transdermal patch; or any drug or substance administered by a suppository, rectal or vaginal; or any drug or substance administered by a subcutaneous implant; or any drug or substance administered orally by a tablet, capsule or ruminal bolus.

The operation of the instant device is predicated on the balancing the relative incompatibilities of the polymer matrix against the vehicle containing the drug in the anhydrous and in the hydrated states. The anhydrous vehicle drug combination should be sufficiently compatible with the polymer matrix such that at elevated temperatures a homogeneous blend is formed which is stable at room temperature. However, the vehicle and drug combination in the hydrated state should be incompatible with the polymer matrix and as a consequence thereof will be expelled from the polymer matrix in the form of a liquid exudate by the process of syneresis. The process of absorbing water into the vehicle is a continuous one, and can be regulated by the selection of the individual vehicle, the rate of expulsion of the vehicle and the drug contained therein. Thus, the exudation at the beneficial agent can be designed to occur over a prolonged period of use. The specific duration of expulsion will vary depending on the use to which the device is put and can extend for a few days, to one year, or even longer.

If the solid polymer (preferably in the form of small particles) is mixed with the plasticizing solvent (with or without dissolved drug) at ambient temperature, a viscous, liquid suspension is formed, which can be cast into any desired shape. If this suspension is now heated to a temperature sufficiently high to fuse or soften the polymer particles, these particles rapidly imbibe the surrounding plasticizing solvent (or solution) and swell to form plastically deformable gel particles which coalesce to yield an essentially homogeneous organogel. On cooling, this gel increases in rigidity, but retains its integrity as a stable, substantially homogeneous, elastically compliant mass.

Polymers or resins suitable for plastisol formulation are those thermoplastics of relatively high fusion- or softening-temperature which exhibit crystallinity, or possess glassy domains which soften only at elevated temperature. Typical examples include poly(vinyl chloride) and its copolymers with vinyl acetate or vinylidene dichloride; natural latex rubbers; polyethylene (both high-and low-density); isotactic polypropylene; poly (styrene, butadiene) block copolymers marketed under the trade name Kraton by Shell Chemical Co.; ethylene/vinyl acetate and ethylene/vinyl alcohol copolymers marketed by duPont under the trade names Elvax and Elvon; polyether- and polyester-based thermoplastic polyurethanes; and block copolymer glycol ether/terephthalate ester thermoplastic elastomers manufactured by duPont.

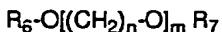
Plasticizing solvents suitable for plastisol formulation are well known to those in the art. They are generally high-boiling liquids of polarity close enough to that of the selected polymer to be capable of swelling or dissolving the polymer at elevated temperature (typically in excess of 140°C), but which will not significantly swell the polymer at ambient temperature. For polyvinyl chloride plastisols, such plasticizers include the esters of aliphatic and aromatic dibasic acids such as dibutyl sebacate and diethyl phthalate; for polyolefins and polymers such as Kraton, paraffinic and naphthenic hydrocarbons are often used.

For the purpose of the present invention, suitable plasticizing solvents must possess additional properties not normally required (and usually undesirable) for conventional plastisols. Firstly, the solvent must be capable of dissolving (and holding in solution at ambient temperature) reasonable amounts of the drug compound of interest; this means that the solvent must possess a solubility parameter not far different from that of the drug in question. The acceptable degree of solubility of the drug in the solvent is quite variable, depending on the potency of the drug, and the desired delivery rate and dosage. The preferred solubility range is probably not less than 5 parts, nor more than 150 parts per 100 parts plasticizing solvent.

Secondly, the plasticizing solvent must be of sufficient polarity (or high enough water solubility) to exhibit at least partial miscibility with water at ambient temperature. The solubility of water in the solvent must be sufficiently high to insure that, when water-saturated, the solvent will cease to be a plasticizing solvent for the polymer. While the water concentration at which solvent compatibility will be lost will vary from polymer to polymer, and solvent to solvent, it is expected that the solubility of water in the solvent (at ambient temperature) should be at least 1% by weight, and preferably greater than 10%; there is no upper limit on solubility.

At the same time, however, the solubility of the drug in the water-saturated solvent must be sufficiently high to assure that precipitation of drug from solution (at ambient temperature) will not occur to any significant extent. The choice of solvent will thus depend not only upon the polymer used, but also upon the water- and organic-solvent solubility of the drug to be incorporated. For PVC-based plastisols, the plasticizing solvents of choice are the alkoxylated polyethylene- or polypropylene glycol ethers (the Dowanols of Dow Chemical); poly(propylene) glycol; block-copolymer polyethylene glycol/polypropylene glycols (BASF-Wyandotte's Pluronics); and the ethoxylated alkylphenols (the Tritons of Rohm and Haas). The ethoxylated fatty acid esters of sorbitan (Tweens and Spans of ICI America) are also candidates. In those instances where the drug- and water-solubility in an otherwise suitable plasticizing solvent are inadequately high, mixtures of two or more such solvents, each of which alone may provide adequate drug- or water-solubility, may be useful.

The preferred vehicle or plasticizing solvent has the following formula:



where R_6 and R_7 are independently hydrogen, alkyl of from 1 to 12 carbon atoms in either a straight, branched or cyclic configuration, phenyl or alkanoyl of from 1 to 6 carbon atoms in either a straight or branched configuration; n is 1 to 5; and m is 1 to 10.

More preferred vehicles are realized in the above formula where R_6 and R_7 are hydrogen, alkyl of from 1 to 6 carbon atoms or phenyl; n is 2 or 3; and m is 2, 3 or 4.

The most preferred vehicles are realized in the above formula when R_6 is butyl, n is 2, m is 2 and R_7 is hydrogen; and when R_6 is methyl, n is 3, m is 2 and R_7 is hydrogen. The first compound is 2-(2-butoxy ethoxy) ethanol or diethylene glycol n-butyl ether which is also identified as Dowanol DB®. The second compound is (2-methoxy-methyl)ethoxy propanol or dipropylene glycol methyl ether which is also identified as Dowanol DPM®. Dowanol DB® and Dowanol DPM® are available from the Dow Chemical Co. of Midland Michigan, USA.

A plastisol formulated from the above three components, when fused at elevated temperature and transformed into an organogel, will consist of a three-dimensional polymer matrix, the interstices of which are filled with a solution of drug in the plasticizing solvent. For conventional organogels (as are used for plasticized PVC products) the volume fraction of plasticizing solvent in the gel is typically in the range of 0.3 to 0.5. For the purpose of this invention, the volume fraction of solvent solution in the gel can be much greater than this, and preferably may be as high as 0.9. The consequences of increasing the volume fraction of plasticizing solvent are to reduce the mechanical strength of the gel, and its stability on aging. These limitations can, however, be minimized by using a polymer of high molecular weight or by mechanically reinforcing the device with a strengthening cover or a mesh reinforcement. Most conventional plastisol PVC resins have molecular weights in the range of 8000 to 300,000 daltons; for the present invention, PVC with higher molecular weights up to 3 million, preferably from 50,000 to 1 million, may be used.

So long as an organogel of the subject invention is kept out of contact with moisture from any source the structure will be stable, and neither plasticizing solvent nor drug will escape from the mass during the normal lifetime of the device (if neither are volatile under these conditions). When, however, such an organogel is exposed to water, or to humid air, a series of events takes place leading to controlled, slow release of drug from the structure; these, in sequence, are as follows:

1. Water molecules migrate into the gel to form a solution of water in the plasticizing solvent; the gel gains weight and swells slightly during this process, but so long as the water content remains low enough to maintain compatibility of the solvent with the polymer, no other changes occur within the gel.

2. As the water content of the plasticizing solvent rises, a water concentration is reached at which the solvent becomes incompatible with the polymer. At that time, the polymer tries to precipitate from the solution, but because it is immobilized in a three-dimensional matrix, this matrix commences to collapse, forming microscopic droplets of (polymer-free) liquid within the gel matrix. The stresses created by the collapsing polymer matrix promote growth and coalescence of these droplets. The elastic stresses in the collapsing polymer network compress the liquid in the pores, and cause its expulsion from the gel at the gel surfaces. This phenomenon, usually referred to as "syneresis" or, "sweating", is a characteristic of unstable gel systems, and is well-documented in the scientific literature.

3. As water is continually imbibed, the syneresing gel continues to shrink and consolidate, expelling the drug-bearing, water absorbed, solvent mixture. As shrinkage proceeds, both the elastic stresses in the network are relieved, and the pore size in the now-microporous matrix decreases. This results in a decline in the rate of expulsion of liquid from the matrix, until finally - when the stresses become insignificant - syneresis ceases. However, in one

embodiment of this invention, the operation of the device has been observed to continue in a constant fashion releasing active agent for a period exceeding 6 months, and durations of up to one year are possible.

In order to assist in the formation of devices such as pet flea and tick collars and to provide additional control in the texture, hardness, flexibility and duration of operation of the device, it may be advantageous to provide, in addition to the plasticizing solvent or vehicle, a plasticizer which is compatible with the solid polymeric macromolecular substance. It should be noted that the vehicle itself can also function as a plasticizer. The plasticizer should be at least partially compatible with the plasticizing solvent and, at least partially compatible with the polymer matrix. The presence of the plasticizer and the amount of plasticizer used can be used to regulate the rate of exudation of the plasticizing solvent and drug mixture as well as the physical properties of the device. Examples of such primary plasticizers are hydrocarbon phthalates (for example diethyl phthalate, diphenyl phthalate, dicyclohexyl phthalate, dimethyl phthalate and dihexyl phthalate); hydrocarbon sebacates (for example dipentyl sebacate, n-butyl benzyl sebacate and dibenzyl sebacate); and hydrocarbon adipates (for example diethyl adipate, dicapryl adipate, di-isobutyl adipate and dinonyl adipate). Other compatible plasticizers are, for example, hydrogenated polyphenols; alkylated aromatic hydrocarbons; and polyester plasticizers, for example polyesters of polyols, such as hexanediol, and poly(carboxylic acids), such as sebacic or adipic acid, having molecular weights of about 2000.

Other materials (for example dyes, pigments, attractants, other biocides, lubricants, fillers, anti-oxidants and ultraviolet stabilizers) may be included in the material. For example, it has been found that the stability of the drug can be extended if a stabilizing amount, preferably 0.1% w to 10% w, of calcium stearate is included in the material. Other stabilizers that may be employed are, for example, bisphenolic and biphenolic stabilizers (for example bis-(3,5-di-tert.butyl-4-hydroxyphenyl)-methane; bis-(2-hydroxy-3-tert.butyl-5-methylphenyl)-methane and 3,3',5,5'-tetra-tert.butyl-4,4'-dihydroxy biphenyl); naphthols (for example beta-naphthol) and benzyl alcohols (for instance 3,5-di-tert.butyl-4-hydroxybenzyl alcohol; 3,5-di-isopropyl-4-hydroxy-benzyl alcohol and 3-methyl-5-tert.butyl-4-hydroxy-benzyl alcohol).

Generally, the drug delivery device is composed of from 10 to 98% of the polymer and from 0 to 70% of the plasticizer, although these ratios may vary widely depending upon the particular nature of the polymer and plasticizer. The vehicle is present in the formulation at from 0.1 to 75% and the drug is present at from 0.1 to 60%. The stabilizer, if used, is present at from 0.1 to 10%. (all percentages are by weight).

Preferably the drug formulation contains from 30 to 70% of the polymer, from 0 to 60% of the plasticizer, from 5 to 50% of the vehicle and from 1 to 50% of the drug.

Most preferably the drug formulation contains from 35 to 60% of the polymer, from 0 to 30% of the plasticizer, from 10 to 45% of the vehicle and from 5 to 40% of the drug.

The instant devices, when used as flea and tick collars are designed to provide for a constant release of drug for a period of at least 6 months and preferably 12 months or even longer. The release rate of the collar will vary considerably depending upon the activity of the particular drug, the nature and the carrier and polymer matrix and the planned duration of the device. These variations can be readily determined by one skilled in the art. Of course, by varying the vehicle, the polymer and the plasticizer, different rates of release of the drug can be achieved.

The components of the instant drug delivery device are mixed and the devices are formed using techniques known to those skilled in polymer manufacture. The devices are formed by combining the ingredients and heating the mixture to a temperature of from 100 to 200°C, preferably from 125 to 160°C, and more preferably from 135 to 160°C, or until a uniform melt is formed whereupon the melted mixture is shaped into the desired articles by the usual technique of casting, extrusion, injection molding and the like. Alternatively, the polymer and the plasticizer can be combined and heated to a melt and the drug and vehicle added thereto, either separately or with the drug predissolved in the vehicle. Since the components of the instant device may be somewhat volatile, depending on the individual plasticizing solvent, plasticizer or polymer selected, it is often advantageous to form the desired objects in a pressurized mold. Pressure is not needed to form the objects themselves, however, only to prevent the loss of volatile components. Thus, the objects themselves need not be pressurized but only the mold in which the objects are formed. Pressures of from 1,000 to 10,000 psi (700,000 to 7,000,000 kg/m²) on the mold are preferred with pressures of 4,000 to 10,000 psi (2,800,000 to 7,000,000 kg/m²) more preferred.

The preferred form of the instant invention is as a flea and tick collar for household pets used as dogs and cats. In such a form the polymeric matrix is molded in the form of an elongated strip of which is 10 to 50 times longer than it is wide. In one embodiment of the invention, the collar is made in a single cross sectional area and shape and of a length which will fit the largest animals contemplated for the use of the collar and the dose for smaller animals is reduced by cutting off the length of the collar in excess of that needed to encircle the neck of the smaller animal.

Since the collars are intended for prolonged durations of use, the collars should be securely fastened to the animal about its neck in such a manner as to prevent its being removed by the normal activities of the animal such as scratching in the area of the collar or the presence of the animal in wooded or overgrown areas. To secure the collar to the animal the collar may be manufactured with a permanently attached buckle, clasp, snap or other attachment means.

The instant device operates by the absorption of water from the environment followed by the synergistic extrusion of drug-containing carrier from the device. When securely affixed about the neck of the animal, the environment, being in

close proximity to the skin and fur of the animal, is in an environment which readily provides the atmospheric water vapor necessary for the operation of the device. However, when the synergistic extrusion occurs, it does so from all surfaces of the collar and, under certain circumstances the extruded drug-containing liquid may not be deposited on the fur and skin of the animal where it can be effective in killing fleas and ticks on the animal, but the liquid may be deposited elsewhere by the animal's activities which may involve rubbing its neck on environmental surfaces, such as bushes, lawns, furniture, carpets, pet owners and the like. This not only reduces the efficiency of the collar but result in drug-containing liquid being deposited in areas where it is not intended to be used.

This can be minimized by partially encasing the collar in a cover which can be installed over from one to three of the elongated surfaces of the collar. The cover will be installed on the collar such like the cover is on the outside and the open surface is in contact with the fur of the animal where the moist environment will ensure the operation of the device, and the normal movements of the animal ensure that the extruded liquid is spread to the fur and skin of the animal.

While the cover will obviously reduce the rate of extrusion of the device since one or more surfaces normally used for extrusion are blocked, this can be overcome by making the collar wider with a larger surface area facing the fur of the animal, or by making the polymeric matrix thinner so that the internal resistance to the flow of the drug and carrier is minimized and the maximum amount of drug is released to the neck of the animal. Alternatively, the composition of the polymeric matrix and/or the hydrophylic carrier can be adjusted for a greater rate of flow.

The cover can be constricted so that it is firmly bonded to the collar to impart strength to the collar-cover system so that there will not be any damage to the system if the collar is scratched by the animal, caught on a branch or other object or abraded by rough objects such as tree bark and the like.

The cover can be constructed in the form of a fiber backing which will impart strength to the collar but have minimal effect on the extrusion rate of the collar. The mesh can be either bonded to the surface or embedded within the collar. Alternatively the cover can be constructed to be completely bonded to at least the outside surface of the collar and optionally the edges of the collar can be similarly covered with a backing material which will seal the surfaces of the collar not directly in contact with the fur of the animal, impart strength to the system and also provide a degree of insulation to the collar. This will provide for a more narrow range of operating temperatures for the collar which would result in a more uniform and predictable rate of extrusion of drug from the collar.

These various aspects of the collar are shown in the accompanying drawings where Figure 1, parts A, B and C show the collar without the installation of fastening means in top, side and edge views.

Figure 2 shows an embodiment of the collar in a top view with a mesh backing (2) to impart strength to the polymeric matrix (1).

Figure 3A shows an embodiment of the collar in enlarged cross section with the polymeric matrix (1) bonded to a cover (3) which is attached only to the outside surface of the collar. Figure 3B shows another version of the collar with the cover (3) attached to the outside and edges of the polymeric matrix (1).

As noted above, the instant drug delivery device can be used in a variety of forms to deliver a beneficial agent or other active agent to a variety of bodily systems. Thus, the selection of the particular beneficial agent to be placed in the device used need not be limited.

The expression, "beneficial agent" as used herein denotes any beneficial agent or compound that can be delivered by the instant device to produce a beneficial and useful result. The term, "beneficial agent" includes biocide, parasiticide, fungicide, larvicide, flukicide, medicine or drug, nutrient, vitamin, food supplement, mineral, anthelmintic, anti-infestation, growth promotant, ionophore, and other agents that benefit the environment of use. In the specification and the accompanying claims the term, "beneficial agent" includes any physiologically or pharmacologically active substances that produce a local or systemic effect in animals, including warm-blooded mammals; humans and primates; household, sport, farm and zoo animals. The term, "physiologically" as used herein denotes the administration of a drug to produce normal levels and functions. The term, "pharmacologically" denotes variations in response to an amount of drug administered to the host. Stedman's Medical Dictionary, 1966, published by Williams and Wilkins, Baltimore, Md. The beneficially active drugs that can be delivered by the instant device include inorganic and organic drugs, such as drugs that act on the central nervous system, depressants, hypnotics, sedatives, psychic energizers, tranquilizers, anticonvulsants, muscle relaxants, antiparkinson agents, analgesic, anti-inflammatory, anesthetics, muscle contractants, antimicrobials, antimalarials, hormonal agents contraceptives, diuretics, sympathomimetics antiparasitics, neoplastics, hypoglycemics, ophthalmics, electrolytes, cardiovascular drugs and the like.

Exemplary drugs that can be delivered by the delivery device are prochlorperazine edisylate, ferrous sulfate, ampicaproic acid, potassium chloride, mecamylamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, benzphetamine hydrochloride, isoproterenol sulfate, methamphetamine hydrochloride, phenmetrazine hydrochloride, bethanechol chloride, methacholine chloride, pilocarpine hydrochloride, atropine sulfate, methscopolamine bromide, isopropamide iodide, tridehexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, oxprenolol hydrochloride, metoprolol tartrate, cimetidine hydrochloride, diphenidol, meclizine hydrochloride, prochlorperazine maleate, phenoxybenzamine, thiethylperazine maleate, anisindone, diphenadione, erythritol tetranitrate, dizoxin, isofurophate, reserpine, acetazolamide, methazolamide, bendroflumethiazide, chlorpropamide, tolazamide, chlormadi-

none acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, progestins, estrogenic steroids, progestational steroids, corticosteroids, hydrocortisone, 17 β -estradiol, ethenyl estradiol, ethynodiol diacetate, prednisolone, hydrocorticosterone acetate, triamcinolone, methyltestosterone, 17 β -hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel, norethindrone, norethisterone, progeterone, norgestrone, norethyndrel, and the like.

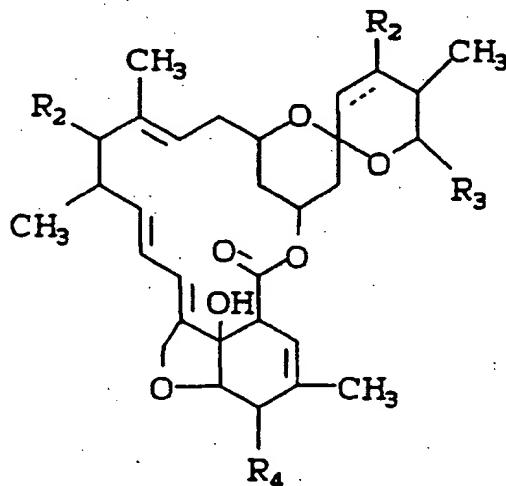
Examples of other beneficial drugs that can be delivered by the delivery device include aspirin, indomethacin, naproxen, fenoprofen, sulindac, diclofenac, indoprofen, nitroglycerin, propanolol, valproate, timolol, atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chloropromazine, reserpine, methyl-dopa, dihydroxyphenylalanine, praloxoxyethyl ester of α -methyldopa hydrochloride, theophylline, calcium gluconate, ferrous lactate, vincamine, diazepam, phenoxybenzamine, blocking agents, and the like. The beneficial drugs are known to the art in Pharmaceutical Sciences, by Remington, 14th Ed., 1979, published by Mack Publishing Co., Easton, Pa.; The Drug; The Nurse, The Patient, Including Current Drug Handbook, 1974-1976, by Falconer et al, published by Sunder Co., Philadelphia, Pa., and Medical Chemistry, 3rd Ed, Vol. 1 & 2, by Burger, published by Wiley-Interscience, New York.

Representative of beneficial medicaments that can be delivered to warm-blooded animals, including ruminants, using the delivery system of this invention, include anthelmintics such as mebendazole, levamisole, albendazole, cambendazole, fenbendazole, parbendazole, oxfendazole, oxybendazole, thiabendazole, tichlorfon, praziquantel, morantel and parantel, and the like; antiparasitic agents such as avermectin and ivermectin, as disclosed in U.S. Pat. Nos. 4,310,519, 4,199,569 and 4,389,397, all assigned to Merck & Co., and in Science, Vol. 221, pp 823-828, 1983, wherein said ivermectin antiparasitic drugs are disclosed as useful for aiding in controlling commonly occurring infestations in animals, such as roundworms, lung worms, and the like, and said ivermectin also being useful for the management of insect infestations such as grub, lice, mange mite, and the like; antimicrobial agents such as chlortetracycline, oxytetracycline, tetracycline, streptomycin, gentamicin, dihydrostreptomycin, bacitracins, erythromycin, ampicillins, penicillins, cephalosporins, and the like; sulfa drugs such as sulfamethazine, sulfathiazole, and the like; growth stimulants such as Monesin® sodium and Elfazepam®; defleating agents such as dexamethazone and flumethazone; rumen fermentation manipulators and ionophores such as lasalocid; virginiamycin, salinomycin and ronnel; minerals and mineral salts; antibloat agents such as organopoly siloxanes; hormone growth supplements such as stilbestrol; vitamins; antienteritis agents such as furazolidone; growth efficiency factors such as β -agonists, clenbuterol, nutritional supplements such as lysine monohydrochloride, methionine, magnesium carbonate, ferrous and ferric compounds, copper oxide, cobalt sulphate, sodium selenite, potassium iodide, zinc oxide and manganese sulphate, and the like; and chemical markers such as chromic oxide, salts of ytterbium and erbium.

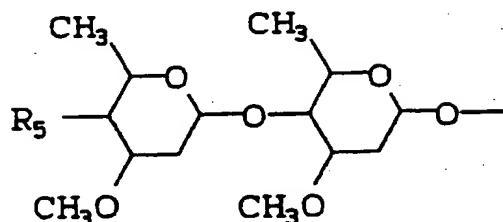
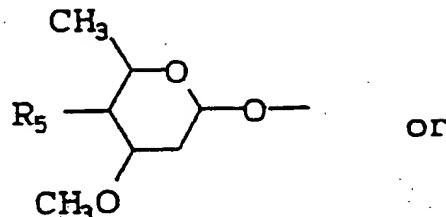
The agents or drugs can be in various forms, such as uncharged molecules, molecular complexes, pharmacologically acceptable salts such as hydrochlorides, hydro-bromide, sulfate laurylate, palmitate, phosphate, nitrate, borate, acetate, maleate, tartrate, oleate, salicylate, and the like. For acid drugs, salts of metals, amines, or organic cations, for example, quaternary ammonium can be used. Derivatives of drugs such as esters, ethers, amides, and the like, can be used. Drugs that are water insoluble can be in form that is converted by enzymes, hydrolyzed by body pH or other metabolic processes, to the original biologically active form.

The term, "animal" is used herein generically denotes any animal such as man, camel; cattle; dog, cat; goat; sheep, swine; deer; bison; giraffe; horse, and elephant.

The preferred beneficial agent or drug to be used in the instant drug delivery device is an active antiparasitic compound or compounds selected from the following generic formula which includes compounds from the avermectin and milbemycin families of compounds.



where R₁ can be H, OH, C₁-C₈-alkoxy, poly C₁-C₈ alkoxy.



25 where the broken line indicates a single or a double bond:

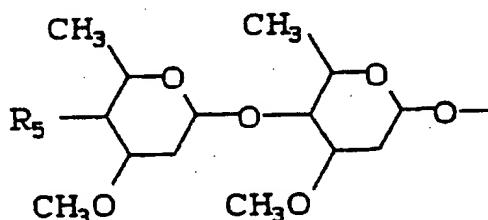
R₂ is is H, OH, -O-C₁-C₈-alkanoyl, C₁-C₈-alkoxy, oxime or substituted oxime where the substituent is C₁-C₈-alkyl, and R₂ is present only when said broken line indicates a single bond;

R₃ is C₁-C₈-alkyl, C₂-C₈-alkenyl, C₃-C₈ cycloalkyl or heterocyclic;

30 R₄ is OH, -O-C₁-C₈-alkanoyl, C₁-C₈-alkoxy, oxime or substituted oxime where the substituent is C₁-C₈-alkyl;

R₅ is OH, -O-C₁-C₈-alkanoyl, =O, amino, substituted amino where the substituents are C₁-C₈-alkyl, C₁-C₈-dialkyl or C₁-C₈-alkanoyl, O-phosphate or O-hemisuccinate.

Preferred compounds for use in the instant dosage delivery device are realized in the above formula where R₁ is
35 hydrogen, poly C₁-C₈-alkoxy or



45 with the broken line indicating a single bond;

R₂ is hydrogen;

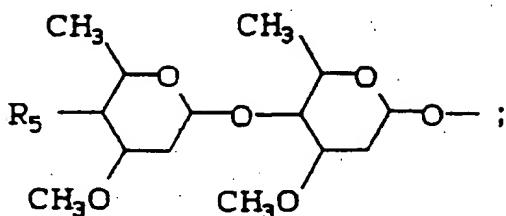
R₃ is is C₁-C₈-alkyl C₂-C₈-alkenyl or C₃-C₈-cycloalkyl;

50 R₄ is OH, C₁-C₈-alkoxy or oxime; and

R₅ is OH, amino, or substituted amino where the substituent is C₁-C₈-alkyl, di-C₁-C₈-alkyl, or C₁-C₈-alkenyl.

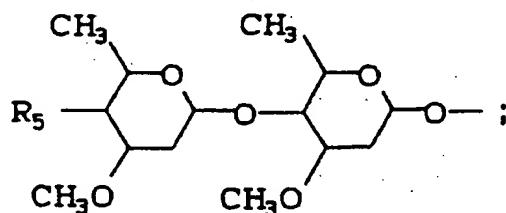
Additional preferred compounds are realized where:

55 R₁ is hydrogen, poly C₁-C₃-alkoxy, or



10 R₂ is hydrogen and a broken line indicates a single bond;
 R₃ is C₃-C₄-alkyl, C₃-C₆-alkenyl or C₅-C₆-cycloalkyl;
 R₄ is hydroxy, C₁-C₃-alkoxy or oxime; and
 R₅ is OH, amino or substituted amino where the substituent is C₁-C₃-alkyl, di-C₁-C₃-alkyl or C₂-C₃-alkanoyl or
 15 C₁-C₃-alkyl-C₂-C₃-alkanoyl.

Still further preferred compounds are realized when R₁ is hydrogen, C₁-C₂ alkoxy-C₁-C₂-alkoxy-C₁-C₂-alkoxy or



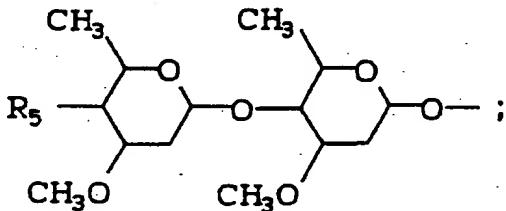
25

30 R₂ is hydrogen and the broken line indicates a single bond;
 R₃ is isopropyl, sec-butyl cyclopentyl or cyclohexyl;
 R₄ is hydroxy, methoxy or oxime; and
 R₅ is OH, amino, N-methylamino, N,N-dimethylamino N-acetyl amino or N-acetyl-N-methylamino.

The most preferred compounds are realized when

35 (1)

R₁ is



45

50 R₂ is hydrogen and its broken line indicates a single bond;
 R₃ is isopropyl or sec-butyl; and
 R₄ is hydroxy.

(2)

55 R₁ is methoxy-ethoxy-methoxy;
 R₂ is hydrogen and the broken line indicates a single bond;
 R₃ is isopropyl or sec-butyl; and
 R₄ is hydroxy.

(3)

R₁ is methoxy-methoxy;
 R₂ is hydrogen and broken line indicates a single bond;
 R₃ is isopropyl or sec-butyl; and
 R₄ is hydroxy.

The following examples are provided in order that the invention may be more fully understood. They are not to be construed as limitative of the invention.

EXAMPLE 1

A polymeric matrix flea collar containing Compound 1, 22,23-dihydro avermectin B1a/B1b (ivermectin) in a PVC polymeric matrix is prepared from the following materials in the following proportions by weight:

Ingredient	Proportion
Polyvinyl chloride powder (GEON 121)	55
Diethyl adipate	8
Calcium stearate	2
Dowanol DB	20
Ivermectin	15

The Dowanol DB and the ivermectin are combined and stirred until solution is achieved. Then the remainder of the materials are added and thoroughly mixed. The liquid mixture is degassed in a vacuum at 25°C for 1 hour. The liquid is then poured into a metal pressurized mold at 140°C and the mold temperature maintained at 140°C and the pressure maintained on the mold at 6,000 psi (4,200,000 kg/m²) for 20 or 30 minutes. The mold is then opened and the solid polymeric matrix flea collar removed.

A sample of the flea collar typically prepared according to the above example in *in vitro* test was developed as a surrogate to the application of a collar to an animal to determine the release rate of the drug from the collar. After the collar was prepared with ivermectin as described above, it is stored in a 50% constant humidity chamber to simulate an environment close to the skin of an animal. Once a day the collar is removed and wiped once with a soft cloth and weighed.

Following such a procedure the collars in the simulated test lost an average 13 to 14 mg per day of the drug plus vehicle for a total area of 122 cm² of the collar and the release rate was seen to be very close to zero-order, that is the collar lost about the same amount each day.

The cumulative weight loss of collars prepared as described above and tested using the surrogate testing procedure is found in the graph of Figure 4 where the Y-axis plots the cumulative weight loss of the collar and the X-axis plots the duration of the test in days. The dimension of the polymeric matrix flea collar is 25.4 x 132 x 4mm and weighed approximately 15g at the start of the test. The solid triangles show the cumulative weight loss for sample heated for 20 minutes and the solid squares show the cumulative weight loss for the sample heated for 30 minutes. The numbers in parentheses are the weights of the samples at the start of the test.

EXAMPLE 2

A polymeric matrix flea collar containing Compound (2) above as the active ingredient (13-methoxy-ethoxy-methoxy-22,23-dihydro avermectin B1a/B1b) is prepared from the following materials in the following proportions:

Ingredient	Proportion
Polyvinyl chloride powder (GEON 121)	50
Diethyl adipate	12
Calcium stearate	2
Dowanol DB	24
Compound (2)	14

Compound 2 is dissolved in the Dowanol DB and the remaining ingredients are combined and mixed thoroughly. The liquid mixture is degassed in vacuo at room temperature for 20 minutes and poured into a metal mold at 140°C. The mold is pressurized to 6,000 psi (4,200,000 kg/m²) and the mold temperature of 140°C maintained for 20 minutes. The mold is opened and the solid collar removed and tested in the surrogate testing procedure described in Example 1. The results of the test are shown for two collars prepared by this procedure in the graph of Figure 5. The release is seen to be substantially linear for a period in excess of 250 days. The open squares and open triangles show the cumulative weight loss for two samples prepared as above (140 C mold temperature and heating time for 20 minutes followed by the weights of the samples at the start of the test).

10 **EXAMPLE 3**

A polymeric matrix flea collar containing Compound (2) as the active ingredient is prepared from the following materials in the following proportions.

15

Ingredient	Proportion
Polyvinyl chloride powder (GEON 121)	52
Calcium stearate	1.5
Butylated hydroxy toluene (BHT) (antioxidant)	0.5
Dowanol DB	32.
Compound 2	14.

25

Compound 2 is dissolved in the Dowanol DB and the rest of the materials added thereto and mixed thoroughly. The liquid mixture is degassed in vacuo at room temperature and poured into a 140°C mold at 6,000 psi (4,200,000 kg/m²) on the mold for 20 minutes as in Example 1 and 2. Several samples of the collar were prepared and some of them were sealed into air and water impervious aluminum lined pouches. The samples were tested in the procedures described in Example 1 with a first collar placed under test on day 0 with the remainder of the samples kept under seal. One sealed package was opened and the collar placed under test on day 18 and a second collar opened and placed under test on day 60. The result of the tests are shown in the graph in Figure 6. The open squares show the cumulative weight loss for the first sample; the open triangles show the cumulative weight loss for the sample unsealed on day 18; and the solid triangles show the cumulative weight loss for the sample unsealed on day 60. The test results show that the samples do not lose any weight until they are exposed to the 50% humidity test conditions since the sealed samples did not gain or lose any weight until they were unsealed. In addition, the samples all showed substantially linear cumulative weight loss with approximately the same slope.

30 **Claims**

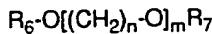
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1. A drug delivery device compounded of a polymeric matrix, a vehicle and a drug such that:
 - a) the polymeric matrix is a linear thermoplastic polymer with a low intrinsic water absorption capability; and where the polymeric matrix is at ambient temperature at least partially resistant to absorption of the vehicle but which will imbibe sufficient quantities of the vehicle at elevated temperature to form a stable homogeneous organogel when cooled to ambient temperature;
 - b) the vehicle is a plasticizing solvent compatible with the polymeric matrix in an anhydrous condition which is fusible in the polymeric matrix at elevated temperature and wherein water is at least 1% soluble by weight in the vehicle and that the vehicle becomes incompatible with the polymeric matrix as water is dissolved therein; and
 - c) the drug is soluble in the vehicle.
2. The drug delivery device of Claim 1 where the polymeric matrix is poly(vinyl chloride) and its copolymers with vinyl acetate or vinylidene dichloride, high and low density polyethylene, isotactic polypropylene, styrene-butadiene block copolymers, ethylene/vinyl acetate and ethylene/vinyl alcohol copolymers, polyether and polyester - based thermoplastic polyurethane or block copolymer glycol ether/terphthalate ester thermoplastic elastomers.
3. The drug delivery device of Claim 2 where the polymer is poly(vinyl chloride).

4. The drug delivery device of Claim 1 where the vehicle has a solubility of water of at least 10% by weight.

5. The drug delivery device of Claim 1 where the vehicle is alkoxyated polyethylene or polypropylene glycol ether, poly(propylene) glycol, block copolymer polyethylene glycol/polypropylene glycols, ethoxyated alkylphenols, ethoxyated fatty acid esters of sorbitan, or mixtures thereof.

6. The drug delivery device of Claim 5 where the vehicle has the formula:



10 where R_6 and R_7 are independently hydrogen, alkyl of from 1 to 12 carbon atoms, phenyl or alkanoyl of from 1 to 6 carbon atoms;
 n is 1 to 5; and
 m is 1 to 10.

15 7. The drug delivery device of Claim 6 where R_6 and R_7 are hydrogen, alkyl of from 1 to 6 carbon atoms or phenyl;
 n is 2 or 3; and
 m is 2, 3 or 4.

20 8. The drug delivery device of Claim 7 where the vehicle is diethylene glycol n-butyl ether or dipropylene glycol methyl ether.

9. The drug delivery device of any one of Claims 1 to 8 which also includes a plasticizer.

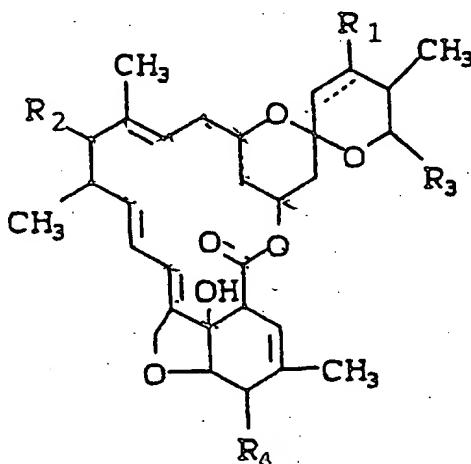
25 10. The drug delivery device of Claim 9 where the plasticizer is a hydrocarbon phthalate, a hydrocarbon sebacate, a hydrocarbon adipate, a hydrogenated polyphenol, alkylated aromatic hydrocarbon, polyester or poly(carboxylic acids).

30 11. The drug delivery device of Claim 10 where the plasticizer is dioctyl phthalate, diphenyl phthalate, dicyclohexyl phthalate, dimethyl phthalate, dihexyl phthalate, dipentyl sebacate, n-butyl benzyl sebacate, dibenzyl sebacate, dioctyl adipate, dicapryl adipate, di-isobutyl adipate or dinonyl adipate.

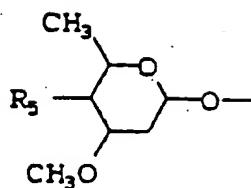
35 12. The drug delivery device of any one of Claims 1 to 11 which is a flea and tick collar for domestic animals.

13. The drug delivery device of any one of Claims 1 to 12 where the drug is an avermectin or a milbemycin.

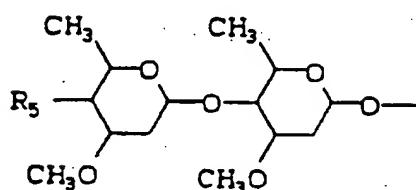
40 14. The drug delivery device of Claim 13 where the drug has the structural formula:



45 50 55 where R_1 can be H, OH, C_1-C_8 -alkoxy, poly C_1-C_8 alkoxy,



or



where the broken line indicates a single or a double bond;

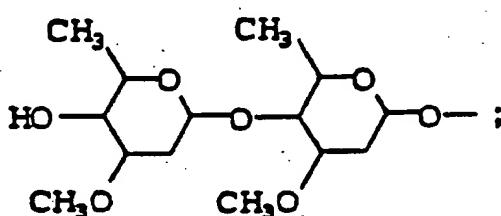
R_2 is H, OH, $-O-C_1-C_8$ -alkanoyl, C_1-C_8 , alkoxy, oxime or substituted oxime where the substituent is C_1-C_8 -alkyl, and is present only when said broken line indicates a single bond;

R₃ is C₁-C₈-alkyl, C₂-C₈-alkenyl, C₃-C₈-cycloalkyl or heterocyclic;

R_4 is OH, O-C₁-C₈-alkanoyl, C₁-C₈-alkoxy, oxime or substituted oxime where the substituent is C₁-C₈-alkyl; and

R_5 is OH, $-O-C_1-C_8\text{-alkanoyl}$, $=O$, amino, substituted amino where the substituents are $C_1\text{-}C_8\text{-alkyl}$, di- $C_1\text{-}C_8\text{-alkyl}$ or $C_1\text{-}C_8\text{-alkanoyl}$, O-phosphate or O-hemisuccinate.

15. The drug delivery device of Claim 14 where B₁ is



R_2 is hydrogen and the broken line indicates a single bond:

R_2 is hydrogen and the broken line

45 R₃ is isopropyl R₄ is hydroxy

16. The drug delivery device of Claim 14 where

B₁ is methoxy-ethoxy-methoxy-

R_3 is hydrogen and the broken line indicates a single bond:

B_2 is isopropyl or sec-butyl; and

H_3 is isopropyl
 B_1 is hydroxy

17. The drug delivery device of Claim 14 where

55

R₁ is methoxy-methoxy:

B- is hydrogen and the broken line indicates a single bond:

R_2 is hydrogen and the broken line
 R_3 is isopropyl or sec-butyl; and

R₃ is isopropyl
R₄ is hydroxyl

18. The slow-release drug delivery device of any one of Claims 1 to 17 which comprises from 10 to 98% of the polymeric macromolecule, from 0 to 70% of the plasticizer, from 0.1 to 75% of the vehicle and from 0.1 to 60% of the drug.

5 19. The slow-release drug delivery device of Claim 18 which comprises from 35 to 60% of the polymeric macromolecule, from 0 to 30% of the plasticizer, from 10 to 45% of the vehicle and from 5 to 40% of the drug.

10 20. A process for the preparation of a drug delivery device as claimed in claim 1, which comprises mixing the matrix-forming thermoplastic polymer with a solution of the drug in the plasticizing solvent at ambient temperature; heating the resulting suspension to a temperature sufficiently high to fuse or soften the thermoplastic polymer; and cooling the gel thereby obtained.

Patentansprüche

15 1. Eine Arzneistoffabgabevorrichtung, compundiert aus einer Polymermatrix, einem Vehikel und einem Arzneistoff, so daß:

- 20 a) die Polymermatrix ein lineares thermoplastisches Polymer mit geringer intrinsischer Fähigkeit zur Wasserabsorption ist, und worin die Polymermatrix bei Umgebungstemperatur wenigstens teilweise beständig gegen Absorption des Vehikels ist, bei erhöhter Temperatur aber ausreichende Mengen des Vehikels aufnehmen wird, um beim Abkühlen auf Umgebungstemperatur ein stabiles homogenes Organogel zu bilden;
- 25 b) das Vehikel ein weichmachendes Lösungsmittel ist, das mit der Polymermatrix in einem wasserfreien Zustand verträglich und bei erhöhter Temperatur in der Polymermatrix schmelzbar ist, und wobei Wasser wenigstens zu 1 Gew.-% in dem Vehikel löslich ist, und daß das Vehikel mit der Polymermatrix unverträglich wird, wenn Wasser darin gelöst wird; und
- c) der Arzneistoff in dem Vehikel löslich ist.

30 2. Die Arzneistoffabgabevorrichtung nach Anspruch 1, worin die Polymermatrix aus Poly(vinylchlorid) und dessen Copolymeren mit Vinylacetat oder Vinylidendichlorid, Nieder- und Hochdruckpolyethylen, isotaktischem Polypropylen, Styrol-Butadien-Blockcopolymeren, Ethylen-Vinylacetat- und Ethylen-Vinylalkohol-Copolymeren, thermoplastischem Polyurethan auf Polyether und Polyesterbasis oder thermoplastischen Glycolether-Terephthalatester-Blockcopolymer-Elastomeren ist.

35 3. Die Arzneistoffabgabevorrichtung nach Anspruch 2, worin das Polymer Poly(vinylchlorid) ist.

4. Die Arzneistoffabgabevorrichtung nach Anspruch 1, worin das Vehikel eine Wasserlöslichkeit von wenigstens 10 Gew.-% hat.

40 5. Die Arzneistoffabgabevorrichtung nach Anspruch 1, worin das Vehikel alkoxylierter Polyethylen- oder Polypropylen-glycolether, Poly(propylen)glycol, Polyethylenglycol-Polypropylenglycole-Blockcopolymer, ethoxylierte Alkylphenole, ethoxylierte Sorbitan-Fettsäureester oder Mischungen davon ist.

6. Die Arzneistoffabgabevorrichtung nach Anspruch 5, worin das Vehikel die Formel:

45
$$R_6-O[(CH_2)_n-O]_m R_7$$

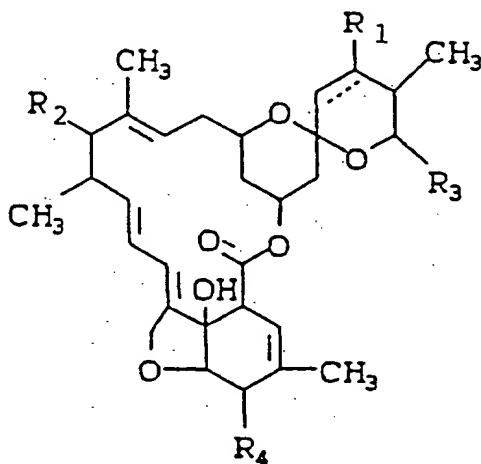
hat, worin R_6 und R_7 unabhängig voneinander Wasserstoff, Alkyl mit 1 bis 12 Kohlenstoffatomen, Phenyl oder Alkanoyl mit 1 bis 6 Kohlenstoffatomen sind,

50 n 1 bis 5 ist, und
m 1 bis 10 ist.

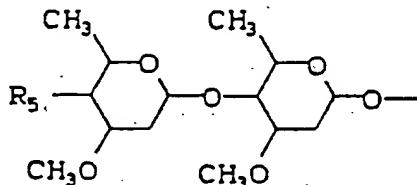
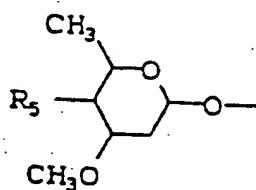
7. Die Arzneistoffabgabevorrichtung nach Anspruch 6, worin R_6 und R_7 Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Phenyl sind,
n 2 oder 3 ist, und
55 m 2, 3 oder 4 ist.

8. Die Arzneistoffabgabevorrichtung nach Anspruch 7, worin das Vehikel Diethylenglycol-n-butylether oder Dipropylenglycolmethylether ist.

9. Die Arzneistoffabgabevorrichtung nach irgendeinem der Ansprüche 1 bis 8, die auch einen Weichmacher enthält.
10. Die Arzneistoffabgabevorrichtung nach Anspruch 9, worin der Weichmacher ein Kohlenwasserstoffphthalat, ein Kohlenwasserstoffsebacat, ein Kohlenwasserstofffadipat, ein hydriertes Polyphenol, alkylierter aromatischer Kohlenwasserstoff, Polyester oder Polycarbonsäuren ist.
11. Die Arzneistoffabgabevorrichtung nach Anspruch 10, worin der Weichmacher Dioctylphthalat, Diphenylphthalat, Dicyclohexylphthalat, Dimethylphthalat, Dihexylphthalat, Dipentylsebacat, n-Butylbenzylsebacat, Dibenzylsebacat, Dioctyladipat, Dicapryladipat, Diisobutyladipat oder Dinonyladipat ist.
12. Die Arzneistoffabgabevorrichtung nach irgendeinem der Ansprüche 1 bis 11, die ein Floh- und Zeckenhalbsband für Haustiere ist.
13. Die Arzneistoffabgabevorrichtung nach irgendeinem der Ansprüche 1 bis 12, worin der Wirkstoff ein Avermectin oder ein Milbemycin ist.
14. Die Arzneistoffabgabevorrichtung nach Anspruch 13, worin der Wirkstoff die Strukturformel:



hat, worin R₁ H, OH, C₁-C₈-Alkoxy, Poly-C₁-C₈-alkoxy,



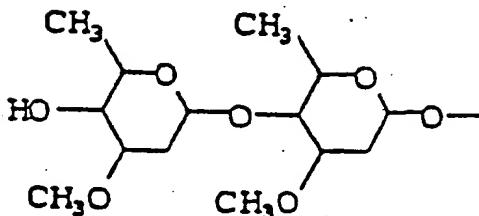
oder

sein kann.

wobei die gestrichelte Linie eine Einfach- oder eine Doppelbindung bedeutet;

50 R₂H, OH, -O-C₁-C₈-Alkanoyl, C₁-C₈-Alkoxy, Oxim oder substituiertes Oxim, worin der Substituent C₁-C₈-Alkyl ist, ist und nur vorhanden ist, wenn diese gestrichelte Linie eine Einfachbindung bedeutet;
 R₃C₁-C₈-Alkyl, C₂-C₈-Alkenyl, C₃-C₈-Cycloalkyl oder heterocyclisch ist;
 R₄OH, O-C₁-C₈-Alkanoyl, C₁-C₈-Alkoxy, Oxim oder substituiertes Oxim, worin der Substituent C₁-C₈-Alkyl ist, ist; und
 55 R₅ ist OH, -O-C₁-C₈-Alkanoyl, =O, Amino, substituiertes Amino, worin die Substituenten sind C₁-C₈-Alkyl, Di-C₁-C₈-Alkyl oder C₁-C₈-Alkanoyl, O-Phosphat oder O-Hemisuccinat.

15. Die Arzneistoffabgabevorrichtung nach Anspruch 14, worin R₁



ist;

15 R₂ Wasserstoff ist, und die gestrichelte Linie eine Einfachbindung bedeutet;
 R₃ Isopropyl oder sek.-Butyl ist; und
 R₄ Hydroxy ist.

16. Die Arzneistoffabgabevorrichtung nach Anspruch 14, worin

20 R₁ Methoxy-Ethoxy-Methoxy ist;
 R₂ Wasserstoff ist, und die gestrichelte Linie eine Einfachbindung bedeutet;
 R₃ Isopropyl oder sek.-Butyl ist; und
 R₄ Hydroxy ist.

25 17. Die Arzneistoffabgabevorrichtung nach Anspruch 14, worin

R₁ Methoxy-Methoxy ist;
 R₂ Wasserstoff ist, und die gestrichelte Linie eine Einfachbindung bedeutet;
 30 R₃ Isopropyl oder sek.-Butyl ist; und
 R₄ Hydroxy ist.

35 18. Die langsam freisetzende Arzneistoffabgabevorrichtung nach irgendeinem der Ansprüche 1 bis 17, die 10 bis 98% des polymeren Makromoleküls, 0 bis 70% des Weichmachers, 0,1 bis 75% des Vehikels und 0,1 bis 60% des Arzneistoffs enthält.

40 19. Die langsam freisetzende Arzneistoffabgabevorrichtung nach Anspruch 18, die 35 bis 60% des polymeren Makromoleküls, 0 bis 30% des Weichmachers, 10 bis 45% des Vehikels und 5 bis 40% des Arzneistoffs enthält.

45 20. Ein Verfahren zur Herstellung einer wie in Anspruch 1 beanspruchten Arzneistoffabgabevorrichtung, das Vermischen des matrixbildenden thermoplastischen Polymers mit einer Lösung des Arzneistoffs in dem weichmachenden Lösungsmitteln bei Umgebungstemperatur, Erhitzen der resultierenden Suspension auf eine Temperatur, die ausreichend hoch ist, um das thermoplastische Polymer zu schmelzen oder zu erweichen, und Abkühlen des dabei erhaltenen Gels umfaßt.

Revendications

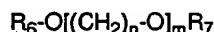
1. Dispositif de libération de médicaments, constitué d'une matrice polymère, d'un véhicule et d'un médicament, tel que :

50 a) la matrice polymère est un polymère thermoplastique linéaire présentant un petit pouvoir intrinsèque d'absorption de l'eau ; et où la matrice polymère présente, à la température ambiante, une résistance au moins partielle à l'absorption du véhicule, mais va s'imprégnner de quantités suffisantes du véhicule à haute température, pour former un organogel homogène stable après refroidissement à la température ambiante ;

55 b) le véhicule est un solvant plastifiant compatible avec la matrice polymère dans des conditions anhydres, qui est fusible dans la matrice polymère à haute température, et où l'eau présente une solubilité d'au moins 1 % en poids dans le véhicule, le véhicule devenant incompatible avec la matrice polymère au fur et à mesure que l'eau s'y dissout ; et

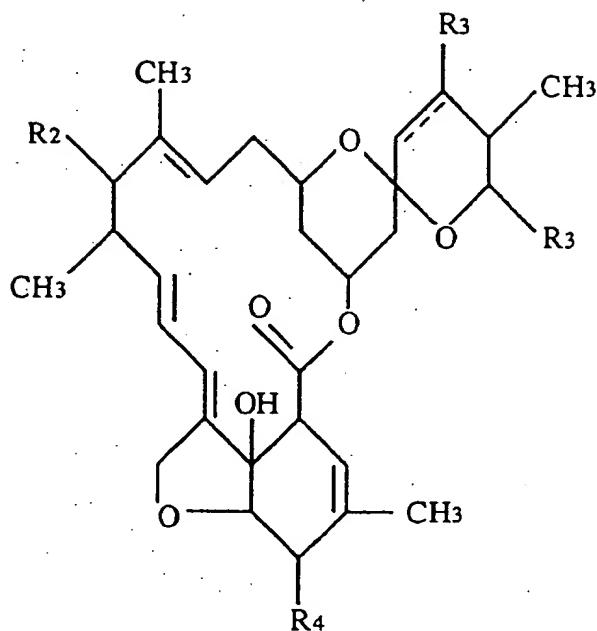
c) le médicament est soluble dans le véhicule.

2. Dispositif de libération de médicaments selon la revendication 1, dans lequel la matrice polymère est constituée de poly(chlorure de vinyle) et de ses copolymères avec l'acétate de vinyle et le dichlorure de vinylidène, de polyéthylène haute densité et basse densité, de polypropylène isotactique, de copolymères séquencés styrènebutadiène, de copolymères éthylène/ acétate de vinyle et éthylène/alcool vinylique, d'un polyuréthane thermoplastique à base d'un polyéther et d'un polyester, ou encore d'élastomères thermoplastiques copolymère séquencé glycoléther/ester téraphthalate.
10. 3. Dispositif de libération de médicaments selon la revendication 2, dans lequel le polymère est le poly-(chlorure de vinyle).
15. 4. Dispositif de libération de médicaments selon la revendication 1, dans lequel la solubilité dans l'eau dans le véhicule est d'au moins 10 % en poids.
5. Dispositif de libération de médicaments selon la revendication 1, dans lequel le véhicule est un éther du polyéthylèneglycol ou du polypropylèneglycol alcoxylé, un poly(propylène)glycol, un copolymère séquencé polyéthylèneglycol/polypropylèneglycol, un alkylphénol éthoxylé, un ester d'acide gras du sorbitan éthoxylé, ou leurs mélanges.
20. 6. Dispositif de libération de médicaments selon la revendication 5, dans lequel le véhicule a la formule

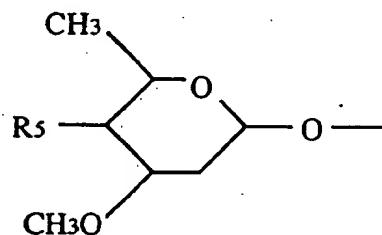


dans laquelle R_6 et R_7 sont chacun, indépendamment l'un de l'autre, un hydrogène, un groupe alkyle ayant de 1 à 12 atomes de carbone, phényle, ou alcanoyle ayant de 1 à 6 atomes de carbone ;
 n vaut de 1 à 5 ; et
 m vaut de 1 à 10.

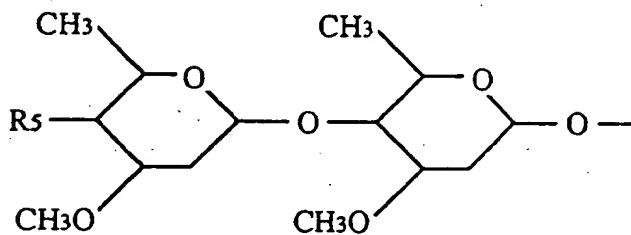
7. Dispositif de libération de médicaments selon la revendication 6, dans lequel R_6 et R_7 sont des hydrogènes, des groupes alkyle ayant de 1 à 6 atomes de carbone ou phényle ;
 n vaut 2 ou 3 ; et
 m vaut 2, 3 ou 4.
8. Dispositif de libération de médicaments selon la revendication 7, dans lequel le véhicule est l'éther n-butylique du diéthylèneglycol ou l'éther méthylique du dipropylèneglycol.
9. Dispositif de libération de médicaments selon l'une quelconque des revendications 1 à 8, qui comprend aussi un plastifiant.
40. 10. Dispositif de libération de médicaments selon la revendication 9, dans lequel le plastifiant est un phtalate hydrocarboné, un sébaçate hydrocarboné, un adipate hydrocarboné, un polyphénol hydrogéné, un hydrocarbure aromatique alkylé, un polyester ou des poly(acides carboxyliques).
45. 11. Dispositif de libération de médicaments selon la revendication 10, dans lequel le plastifiant est le phtalate de diocytyle, le phtalate de diphenyle, le phtalate de dicyclohexyle, le phtalate de diméthyle, le phtalate de dihexyle, le sébaçate de dipentyle, le sébaçate de n-butylbenzyle, le sébaçate de dibenzyle, l'adipate de dioctyle, l'adipate de dicapryle, l'adipate de diisobutyle ou l'adipate de dinonyle.
50. 12. Dispositif de libération de médicaments selon l'une quelconque des revendications 1 à 11, qui est un collier anti-puces et anti-tiques pour animaux domestiques.
13. Dispositif de libération de médicaments selon l'une quelconque des revendications 1 à 12, dans lequel le médicament est une avermectine ou une milbémycine.
55. 14. Dispositif de libération de médicaments selon la revendication 13, dans lequel le médicament a la formule développée suivante :



25 dans laquelle R₁ peut être H, OH, un groupe alcoxy en C₁-C₈, poly(alcoxy en C₁-C₈).



ou



où la ligne en tirets indique une simple liaison ou une double liaison;

50 R₂ est H, OH, ou un groupe -O-(alcanoyle en C₁-C₈), alcoxy en C₁-C₈, oxime ou oxime substitué où le substituant est un groupe alkyle en C₁-C₈, et n'est présent que quand ladite ligne en tirets indique une simple liaison;

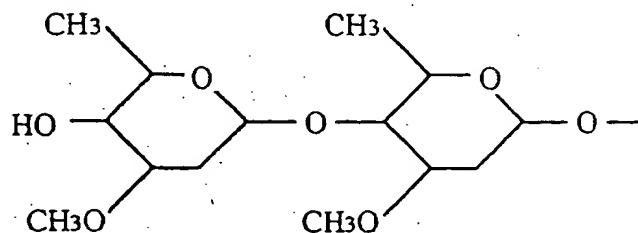
R₃ est un groupe alkyle en C₁-C₈, alcényle en C₂-C₈, cycloalkyle en C₃-C₈ ou hétérocyclique;

55 R₄ est OH ou un groupe -O-(alcanoyle en C₁-C₈), alcoxy en C₁-C₈, oxime ou oxime substitué où le substituant est un groupe alkyle en C₁-C₈ ; et

R_5 est OH ou un groupe -O-(alcanoyle en C₁-C₈), =O, amino, amino substitué où les substituants sont des groupes alkyle en C₁-C₈, di-(alkyle en C₁-C₈) ou alcanoyle en C₁-C₈, O-phosphate ou O-hémisuccinate.

15. Dispositif de libération de médicaments selon la revendication 14, dans lequel

R₁ est



R₂ est un hydrogène et la ligne en tirets indique une simple liaison ;

R₃ est le groupe isopropyle ou sec-butyle ; et

R₄ est le groupe hydroxy.

16. Dispositif de libération de médicaments selon la revendication 14, dans lequel

R₁ est le groupe méthoxy-éthoxy-méthoxy;

R₂ est un hydrogène et la ligne en tirets indique une simple liaison ;

R₃ est le groupe isopropyle ou sec-butyle ; et

R₄ est le groupe hydroxy.

25 17. Dispositif de libération de médicaments selon la revendication 14, dans lequel

R₁ est le groupe méthoxy-méthoxy ;

R₂ est un hydrogène et la ligne en tirets indique une simple liaison ;

R₃ est le groupe isopropyle ou sec-butyle ; et

R₄ est le groupe hydroxy.

30 18. Dispositif de libération retard de médicaments selon l'une quelconque des revendications 1 à 17, qui comprend de 10 à 98 % de la macromolécule polymère, de 0 à 70 % du plastifiant, de 0,1 à 75 % du véhicule et de 0,1 à 60 % du médicament.

35 19. Dispositif de libération retard de médicaments selon la revendication 18, qui comprend de 35 à 60 % de la macromolécule polymère, de 0 à 30 % du plastifiant, de 10 à 45 % du véhicule et de 5 à 40 % du médicament.

40 20. Procédé pour préparer un dispositif de libération de médicaments selon la revendication 1, qui consiste à mélanger le polymère thermoplastique formant matrice à une solution du médicament dans le solvant plastifiant à la température ambiante ; à chauffer la suspension obtenue à une température suffisamment élevée pour faire fondre ou ramollir le polymère thermoplastique ; et à refroidir le gel ainsi obtenu.

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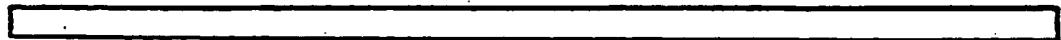
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Figure 1

A



B



C

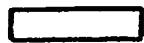


Figure 2

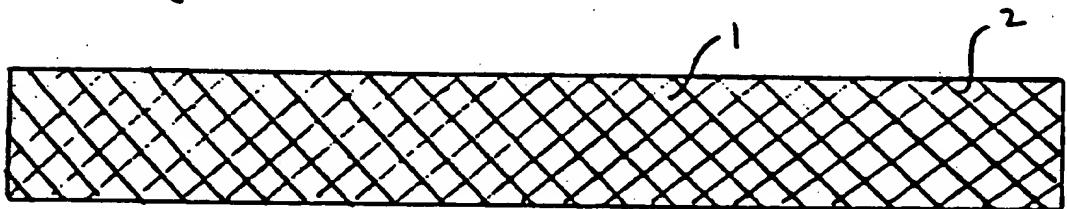


Figure 3

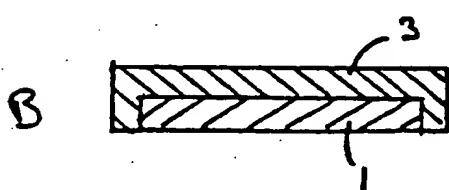
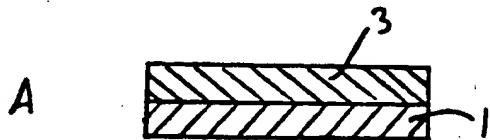


FIGURE 4
CUMULATIVE WEIGHT LOSS

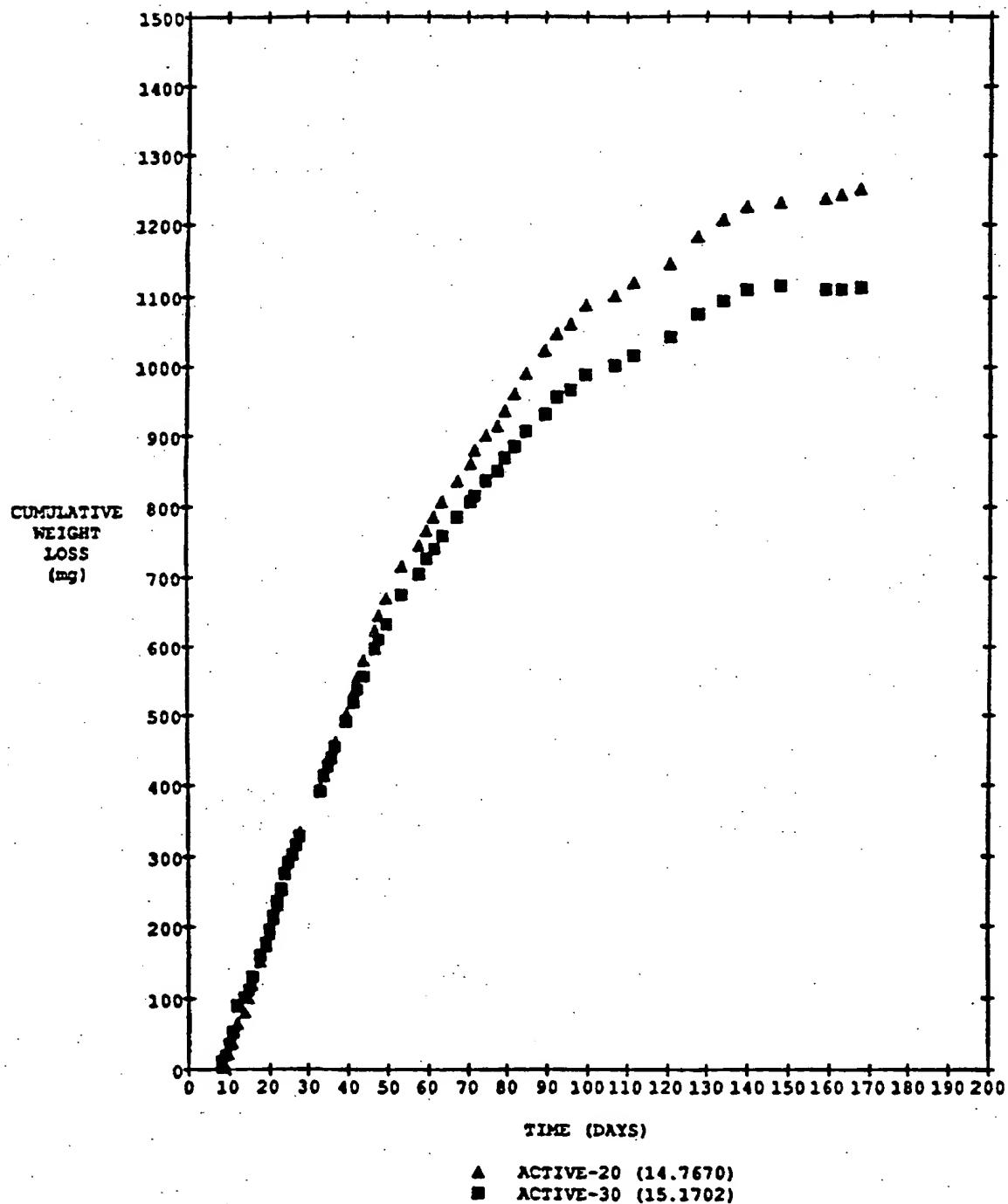


FIGURE 5
CUMULATIVE WEIGHT LOSS

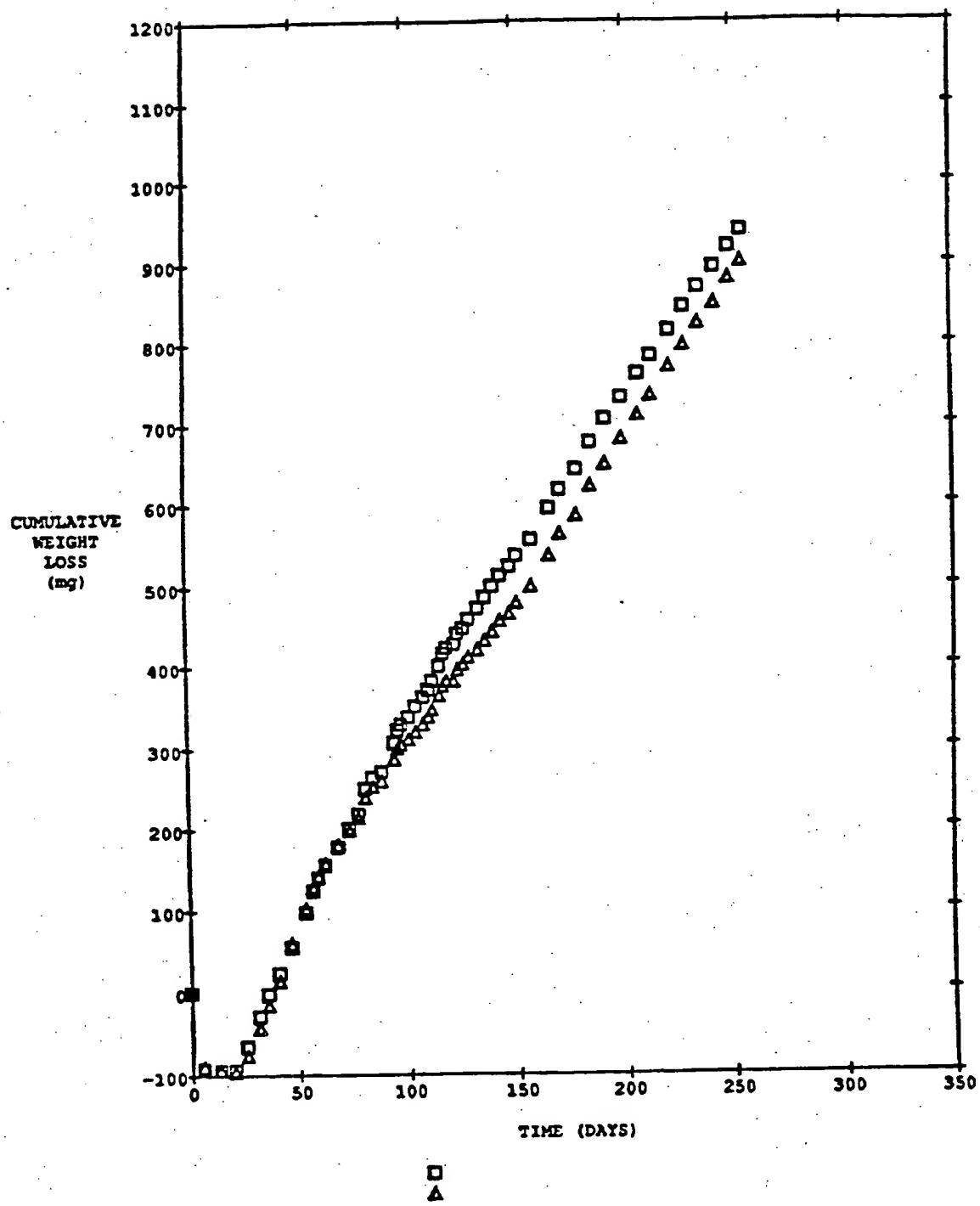
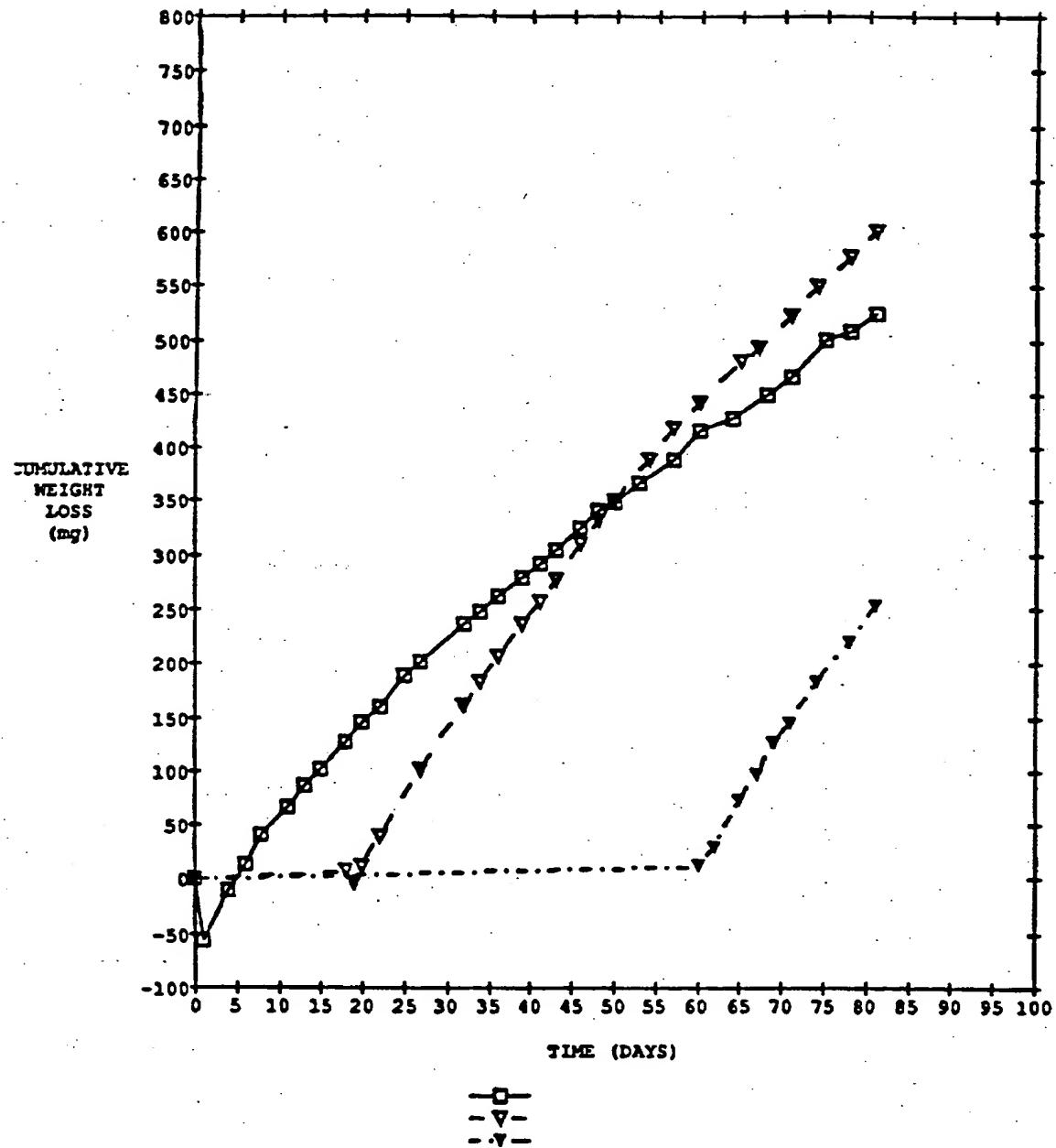


FIGURE 6
CUMULATIVE WEIGHT LOSS



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